Efficacy of exercise training in patients with HFpEF

NCT04506606

November 25,2020

VA Consent Document

DESCRIPTION OF RESEARCH BY INVESTIGATOR

Concise Summary

We have summarized the most important information about this research study at the beginning of this consent form. More details are included after this summary.

You are being invited to take part in a research study because you either have heart failure or are a healthy person of similar age who is serving as a comparison (called a control). Heart failure is a condition where the heart and blood vessels have trouble pumping enough blood to the body.
Taking part in this study is your choice.

The purpose of this study is to learn how sensors in the muscles affect the heart and tiredness during exercise in people with heart failure. We are also studying how well a standard cardiac rehabilitation program can improve these effects.

If you choose to take part, you will be asked to visit our research lab several times. During these visits, you will perform a leg exercise called knee extension. At two of these visits, you will receive an injection in your back. This injection contains medicine that reduces the signals from the muscle sensors before you begin the exercise. During these visits, we will also check your blood pressure and collect small blood samples before, during, and after the exercise. We will also test your muscles before and after exercise to see how tired they become. These procedures will be explained in more detail later in this document.

There may be some risks and discomfort from the injection and from the small tube used to collect blood. There may also be some risks related to the exercise and the tests we use to measure tiredness. These risks will be described more fully later in this document. You might benefit from being in the study, but there is no promise of benefits. You may also help others in the future by being part of this research study. There are no alternative procedures to those in this document. Following your enrollment, we expect you to be done with the study within 7-9 weeks. The study procedures will be discussed in detail later in this form.

You can take this form home to read or talk about it with your family before deciding. Please take your time and read the information carefully. Ask the research staff if you have any questions or if something is not clear. If you agree to join the study, you will be asked to sign this form. The consent process and the study will take place at the Salt Lake City Veterans Affairs Medical Center.

GENERAL OUTLINE:

- **Experimental visit 1**: You will complete a preliminary screening and become familiar with the lab and equipment. You will also do an exercise test to measure your maximum oxygen use ($\dot{V}O_2max$). (~2 hours)

- **Experimental visit 2**: We will test your heart and blood vessel function. You will also practice the knee extensor exercise and related procedures (~3 hours)
- **Experimental visit 3**: You will be tested for of blood pressure and breathing sensitivity **(**~3.5 hours)
- **Experimental visit 4**: You will perform knee extension exercise at four effort levels below your maximum—once under normal conditions and once with blocked muscle nerve feedback. (~7 hours)
- **Exercise training visits: 1-24**: You will take part in a supervised exercise training program, using one-legged knee extension exercises.
- **Experimental visit 5**: We will re-test your cardiac and vascular function, and you will again practice knee extension exercise procedures. (~2 hours)
- **Experimental visit 6**: You will be tested for blood pressure and breathing sensitivity **(**~3.5 hours).
- **Experimental visit 7**: You will repeat the knee extensor exercise at four submaximal levels, under both normal and blocked nerve feedback conditions.(~7 hours).
- **Experimental visit 8**: You will do a final bike exercise test to measure your whole-body $\dot{V}O_2$max again (~1 hour)

STUDY PROCEDURES
Participating groups: Heart failure and age matched healthy controls (ages 18-85).

Experimental visit 1: Preliminary screening and maximal exercise test (~2 hours):

1. You will be asked some questions about your health, like your age, if you smoke, your family's health history, your cholesterol levels, and how active you are. You don't have to answer any questions that make you feel uncomfortable. You will also fill out a short survey called the PHQ-9. It asks about how often you've felt sad or had other signs of depression in the last two weeks. This study may have unknown risks for people who are pregnant or fetuses. If you can get pregnant, you will take a urine pregnancy test at the start of the study. If you find out you are pregnant during the study, you must tell the main researcher or study staff right away.

2. We will take a small sample of blood (up to 2 teaspoons) from a vein in your arm. Blood will be collected in a clean setting by trained staff. Your safety is very important to us during this process. To help prevent infection and keep everything safe, we will clean the area on your arm with alcohol before the blood draw, use a new sterile needle and syringe for each person, and staff will wear new disposable gloves for each participant.

3. We will measure your blood pressure using a blood pressure monitor. This device has a cuff that wraps around your arm and a small digital machine. The cuff will automatically fill with air and squeeze your arm. Then, the pressure will slowly release while the machine measures your blood pressure.

4. You will be asked to wear a small device called an **accelerometer** or pedometer on your wrist, arm, waist, or leg for 7 to 14 days. This device will track how active you are and record how many calories you burn during your normal daily activities. You will need to bring the device back at your next visit. If the device is lost, stolen, or damaged, you will not have to pay for it.

5. You may be asked to wear a **24-hour blood pressure monitor**. This is an automatic device that measures your blood pressure throughout the day and night. For example, it may take a reading every 30 minutes during the day (from 8:00 am to 8:00 pm) and every hour during the night (from 8:00 pm to 8:00 am). Or, it may take a reading every 15 minutes during the day (from 6:00 am to 10:00 pm) and every 20 minutes at night.

6. You will be asked to do a **6-minute walk test (6MWT)**. For this test, you will walk as fast as you can for 6 minutes while we measure how far you walk. You may also be asked to do some balance tests. After that, we will measure how quickly you can stand up from a seated position and how fast you can walk a short distance of 30 feet.

7. Exercise: You may be asked to exercise on a stationary bike until you cannot continue. Your goal will be to pedal at about 75 revolutions per minute. This is called a progressive ergometer test. The exercise will get harder every minute until you have to stop. A doctor involved with the study will be available for older and patient populations.

8. Cardiopulmonary measures: During this test, you will breathe through a mouthpiece so we can measure how much air you breathe and the gases in your breath. You'll also wear a cuff on your finger. At times, you'll switch from breathing normal room air to breathing from a bag. You'll take about 8 to 16 normal breaths from the bag, then go back to breathing room air. These tests help us figure out how much blood your heart is pumping each minute. This is called non-invasive cardiac output, or NICO. Wires attached to small sticky pads on your chest will be used to check your heart rate. Another sticky pad may be placed on your forehead to help measure how much oxygen is in your blood. Your blood pressure will be checked with a cuff on your arm or finger while you exercise. We will also ask you how hard it feels to breathe and how tired your legs feel during the test. In some cases, we may use a special light-based tool (called near-infrared spectroscopy) to measure how much oxygen is in your muscles, without using needles. A doctor involved with the study will be available for older participants.

9. Neuromuscular measures: While you are sitting, we will ask you to push your ankle forward as hard as you can against something that does not move. This helps us measure how well your brain and nerves can tell your muscles to contract. To do this, we will send small electrical signals to the nerve that controls your thigh muscles. This is called **femoral nerve stimulation (FNS)**. We will also place small sticky sensors (called surface electrodes) on your skin to measure your muscle's electrical activity. We will use these tools to measure how tired your thigh muscles (quadriceps) become. These tests may be done before, during, and after the exercise.

Experimental visit 2: Vascular Function and One-legged exercise test (~3 hours):

1. You will be asked not to eat or drink anything (except water) for up to 12 hours before coming to the lab. You will also need to keep fasting during your visit. We will take a small blood sample (up to 2 teaspoons of blood) from a vein in your arm.

2. *Echocardiogram:* This test uses ultrasound (sound waves) to create pictures that show how your heart muscle and valves are working. A trained sonographer will perform this test to check the shape and function of your heart.

3. Vascular function: We will check how well your blood vessels are working using two tests: **flow-mediated vasodilation (FMD)** and **passive leg movement (PLM).** For the FMD test, you will lie down while a blood pressure cuff is placed on your arm (near your elbow) and/or your leg (near your knee). The cuff will be pumped up to a high pressure for about 5 minutes. This will temporarily stop blood flow to your lower arm or leg. You may feel a tingling or numb sensation in your hand or foot while the cuff is inflated. After about 5 minutes, the cuff will be released, and blood will flow back into the area. This test also gives us extra information about your small blood vessels, called **reactive hyperemia (RH)**, which helps us understand how healthy your blood vessels are. For the PLM test, a member of the research team will gently move your leg back and forth at the knee joint. This movement may last from a few seconds to up to 3 minutes (1 to 180 seconds).

4. We may also do some extra tests to check how flexible your blood vessels are. These tests are non-invasive, which means they do not involve needles or go inside your body. For the **pulse-wave velocity (PWV) test**, we will place a blood pressure cuff on your thigh and a small sensor on your neck. This will help us measure how fast blood moves through your arteries. For the **ankle-brachial index test**, we will use a blood pressure cuff and a Doppler ultrasound device to measure blood pressure in your arm and ankle. This helps us understand how well blood is flowing to your legs. For the **carotid intima thickness test**, we will use Doppler ultrasound to take a picture of a blood vessel in your neck. This helps us check the thickness of the blood vessel wall, which gives us information about your heart and blood vessel health.

5. *Exercise:* You will take part in an exercise test while sitting down. You will use a machine called a knee extensor ergometer. This device lets you kick your leg forward to work your thigh muscles, then it brings your leg back to a bent position on its own. During the test, you will try to do 60 leg extensions per minute. The exercise will continue until you can no longer keep up with at least 50 leg extensions per minute. This is called a progressive ergometer test. As the test goes on, the exercise will get harder every minute until you are too tired to continue. A doctor involved with the study will be available for older and patient populations.

6. At rest and during exercise we will measure variables mentioned in Experimental visit 1 under *Cardiopulmonary measurements* and *Neuromuscular measurements.*

7. You may need to come to the lab for extra visits (Experimental Visit 3 and 4) to practice and make sure the measurements are consistent each time.

Experimental visit 3: Baroreflex and chemoreflex sensitivity (~3.5 hour):

1. You will be asked not to eat or drink anything (except water) for up to 12 hours before coming to the lab. You will also need to keep fasting during your visit. A small, flexible tube called an arterial catheter will be

placed in an artery in your forearm (called the radial artery). Another small tube, called a venous catheter, will be placed in a vein in your arm where it bends (the antecubital vein). A member of the research team will put in the venous catheter. This tube will be used to give you drugs that affect your blood pressure (explained more in step #3). The arterial catheter will let us directly measure your blood pressure and take blood samples. These samples help us check the amount of gases like oxygen and carbon dioxide in your blood, along with other things. A doctor called an anesthesiologist will place the arterial catheter using very clean and careful methods to avoid infection. The doctor will wear special sterile clothes, and the skin where the catheter goes in will be cleaned with an antiseptic to kill germs. Before placing the catheter, the doctor will numb the area by injecting a drug so you won't feel pain.

2. You will be asked to sit or lie back and to relax as much as possible. While you rest, we will watch your breathing using a mouthpiece. During this time, you will breathe different mixtures of gases to change the levels of oxygen and carbon dioxide in your body. You will not be told when or which gases you're breathing..

3. We will give you small amounts of two different drugs to see how your body reacts to changes in blood pressure. This is called the "Modified Oxford Technique."
    - First, we will inject a drug called **Phenylephrine (PE)**. It works like a chemical your body naturally makes. It makes your blood vessels smaller, which will raise your blood pressure by about 15 points.
    - Next, we will inject a small amount of a drug called **Sodium Nitroprusside (SNP)**. This drug does the opposite—it makes your blood vessels bigger and lowers your blood pressure by about 15 points.
    - Each drug will be given 2 or 3 times, and each dose will last about 30 seconds.

4. We will use a technique called **microneurography** to find a nerve in your arm or leg to measure nerve activity.
    - First, we'll find the nerve by gently pressing on the area and using an ultrasound machine. In the arm, the nerve will be either halfway between your shoulder and elbow or near the bend in your arm. In the leg, the nerve will be just below the outside of your knee. We may use a very small electric current (less than 4 volts) through a pencil-shaped tool placed on your skin. This may cause your arm or leg to twitch or tingle a little, but that will stop when the current is turned off.
    - Once we find the nerve, we will place two tiny, sterile needle-like wires (called electrodes) through the skin in your arm or leg. One will go just above the nerve, and the other will go into the nerve to record signals. This will be done using ultrasound to guide placement. When the recording wire touches the nerve, you may feel a small muscle twitch or tingling, which is normal. We'll make a few small adjustments to get a clear signal. This nerve signal is called **muscle sympathetic nerve activity (MSNA).**

5. You will be asked to lie quietly for 20 minutes while we measure your **heart rate variability (HRV)**, which is the number of times your heart rate increases and decreases.

6. You will be asked to do several rounds of **handgrip exercise**. First, you will squeeze a special handle as hard as you can to find your strongest grip. Then, for the exercise, you will squeeze a padded handle either once every second or every two seconds for about 3 to 6 minutes. Sometimes, you may need to squeeze the handle continuously for 2 to 5 minutes. At the end of each exercise, we might put a blood pressure cuff on your arm and inflate it to a high pressure for 2 to 3 minutes. If you need to, you can rest for 5 to 10 minutes between each round.

You will be asked to do several rounds of knee extensor (KE) exercise. This means you will kick your leg once every second for about 3 to 6 minutes. If you need to, you can rest for 5 to 10 minutes between each round. While you do the exercise, we will use an ultrasound machine to measure the blood flow in the femoral artery (a large blood vessel in your thigh).

Experimental visit 4: One-legged exercise test (~7 hours):

1. You will be asked not to eat or drink anything (except water) for up to 12 hours before coming to the lab. You will also need to keep fasting during your visit. A small tube, called a catheter, will be placed into an artery and vein in your leg. These are blood vessels that carry blood to and from your body The catheters will help us measure your blood pressure directly and collect blood samples. We will test the blood to see how much oxygen and carbon dioxide it has, along with other things. A trained doctor (anesthesiologist) will place the catheters using sterile procedures to prevent infection. The doctor will wear sterile clothing and chlorhexidine gluconate will be rubbed on the skin to remove germs. Before putting in the catheter, the doctor will numb the area with a local anesthetic (a medicine to prevent pain).

2. *Exercise*: One-legged knee-extensors exercise , same as on Experimental visit 3.

3. At rest and during exercise we will measure variables mentioned in Experimental visit 1 under *Cardiopulmonary measurements* and *Neuromuscular measurements*.

4. No physical activity will be allowed for 2 hours following the 4th exercise session.

5. After the resting period, you will perform the same *Exercise, Cardiopulmonary measurements,* and *Neuromuscular measurements* as before you rested, but after the injection of a numbing solution (intrathecal fentanyl). A trained doctor (anesthesiologist) will inject a numbing medicine into your lower back. This will temporarily reduce the signals between your leg muscles and your brain while you exercise. The needle goes into the space around your spinal cord, but the procedure is not painful, and you will still be able to move and feel normally overall. The numbing effect will begin to wear off after about 1 hour and should be completely gone within 2 hours. You will need to stay in the lab until the medicine fully wears off—this could take up to 3 hours total. You will also be asked to squeeze a device (like a handgrip) before and after the injection. This helps us measure your heart rate and blood pressure.

6. We may take a small sample of muscle from your thigh, called a **muscle biopsy**. Before the sample is taken, we will numb the area with a local anesthetic called lidocaine, so you should not feel pain during the

procedure. A small cut (incision) will be made to collect the muscle sample. This may be done 2 to 3 times to make sure we get enough tissue for testing. Taking part in the muscle biopsy is completely optional. If you choose not to have the muscle biopsy, you can still be part of the study and complete all other parts of the research.

Exercise training visits 1-24: Exercise training (~1 hour/session):

1. You will be asked to complete 24 sessions of a supervised exercise program. Each session will last between 30 to 60 minutes and will involve exercising one leg at a time using the knee extension machine. The difficulty of the exercise will change from session to session. This helps make sure your muscles are getting the right kind of challenge to improve over time.

Experimental visit 5: Vascular Function and One-legged exercise test(~2 hour):

1. You will perform the same procedures from Experimental visit 2

Experimental visit 6: Baroreflex and chemoreflex sensitivity (~3.5 hours):

1. You will perform the same procedures from Experimental visit 3

Experimental visit 7: One-legged exercise test (~7 hours):

1. You will perform the same procedures from Experimental visit 4.

Experimental visit 8: Maximal exercise test (~1 hour):

1. You will perform the same procedures from Experimental visit 1.

RISKS

Blood draw:
There is a possibility of bruising from blood draws. All blood draws will take place in a clean setting and will be done by trained staff. Your safety is very important. To help prevent infection, the area where the tube goes in will be cleaned with alcohol, and new, sterile needles and gloves will be used for each person.

Breathing gas mixtures (i.e. chemoreflex sensitivity):
When you breathe in different gases to change the oxygen and carbon dioxide levels in your body, you might breathe faster and feel short of breath. You could also feel sleepy, dizzy, nauseous, or get a headache. More serious problems, like confusion, seeing things that aren't there, or fainting, are very rare in this test. The number of breaths you take with these gases will start small and slowly increase to make sure your oxygen level (called SpO2) doesn't go below 75%, to keep you safe. Breathing 100% nitrogen (N2) will only lower your oxygen for a short time, and your oxygen levels will go back to normal once you start breathing normal air again. Your breathing and heart responses will be watched the whole time. You will be able to leave when your oxygen levels before and after the test are about the same. Other than lowering oxygen, breathing nitrogen gas does not cause any

other risks. If your oxygen level stays low after breathing normal air, you will be given extra oxygen until your oxygen level is no longer low.

Catheter:
Putting a small plastic tube, called a catheter, into an artery or vein in your arm (like the radial artery or antecubital vein) or leg (like the femoral artery or femoral vein) has a small risk of causing problems. After the tube is taken out, you might get an infection, swelling, or pain where it was placed. You could also feel dizzy, faint, or have bruising from the catheter being put in. In rare cases, a blood clot can form in a deep vein. This is called deep vein thrombosis (DVT). If the clot moves to your lungs, it can cause a serious problem called a pulmonary embolism. To lower these risks, the catheter will be cleaned with a special fluid called heparin that stops blood clots from forming.

Drug injection risks (i.e. baroreflex sensitivity):
The injection of phenylephrine (PE) and sodium nitroprusside (SNP) will make your blood pressure go up and down, respectively. We will use low doses of both drugs to avoid big changes in your blood pressure. Your blood pressure, heart rate, heartbeats (R-R intervals), and how much blood your heart pumps will be recorded continuously. The doses of these drugs will be slowly increased to make sure your blood pressure doesn't go up or down more than 15 mmHg during each injection. If your blood pressure gets too low, you might feel light-headed or faint. The rise in blood pressure during this test is similar to what happens during exercise and has a low risk. To keep you safe, all the procedures will be done while you are sitting or leaning back. This method has been used a lot in research to study how the body controls blood pressure.

Echocardiogram:
An external echocardiogram is safe and noninvasive, meaning it does not go inside your body. Some people may feel a little uncomfortable from staying in one position during the test.

Electrical stimulation of the femoral nerve (FNS):
We will use small electrical pulses to make your thigh muscles (quadriceps) contract. This is done by placing a small, round electrode (about the size of a quarter) on the skin near your groin. This method is safe and does not involve needles. The electrical pulses are very short and delivered at different strengths and speeds to find the strongest muscle response, called Mmax. You might feel brief discomfort during the stimulation, and your skin and muscles may twitch, but it won't cause any lasting harm. This type of test is commonly used in research on the nervous system and has been shown to be safe. The equipment is FDA-approved, and there is no risk of electric shock because the stimulators use medical-grade, isolated power sources.

Exercise:
There is a very small risk that exercise/strength training could show a hidden heart problem, particularly with the blood vessels which supply the heart (coronary arteries). This could include things like not enough blood getting to the heart (myocardial ischemia), a heart attack (myocardial infarction), or an irregular heartbeat (arrhythmia), and these serious heart problems could be life-threatening. Signs of a heart problem might include chest pain, feeling very short of breath, or unusual results on a heart test called an ECG (electrocardiogram), during exercise. The ECG is done to help make sure your heart is safe while you exercise.

If any signs of a problem show up, the exercise will be stopped right away, and you'll be referred to your regular doctor for care.

Also, it's normal to have some muscle soreness after exercise. This might last for a few days
You are free to indicate any discomfort and discontinue participation at any time.

Intrathecal fentanyl:
Post-Spinal Headache: Some people (0–9%, and very rarely up to 24%) may get what's called a "spinal headache" after the procedure. This happens when spinal fluid leaks and causes pressure changes around the brain. These headaches usually happen soon after the procedure and often go away by drinking fluids, especially ones with caffeine. If the headache doesn't go away, doctors may treat it with IV fluids or caffeine, or by doing a "blood patch." That means they take a small amount of your own blood and inject it near the spine to seal the leak. Almost everyone who gets a blood patch feels better within 1–2 hours. In our past studies, we've used intrathecal fentanyl in over 50 volunteers without any cases of spinal headaches.

Nerve Damage: Very rarely, if a blood vessel is hit during the procedure, a pocket of blood (called a hematoma) could form and press on the spinal cord, possibly causing nerve damage. This is extremely rare. Nerve problems might feel like tingling, prickling, numbness, burning, or weakness. Out of about 40,000 patients in other studies, only 24 had nerve-related issues, most of which were mild. In our own studies, we've used spinal anesthesia in over 50 volunteers without any cases of nerve damage.

Death or Paralysis: The chances of dying or being paralyzed from spinal anesthesia are extremely low—less than 1 in 200,000.

Other Risks: There are other risks associated with spinal anesthesia. These include, but are not limited to, trouble peeing, infection, back pain, accidental injection of medication into a blood vessel, slowed breathing, itching, nausea, and meningitis (a serious infection around the brain and spine). Again, these risks are very rare. Emergency medicine will be available if needed.

Loss of Confidentiality:
Although research records will be stored in a secured area and participant confidentiality will be maintained by the investigative team, there is a small risk of loss of confidentiality because this study involves the use of identifiable data.

Muscle Biopsy:
A small cut (about 1/8 inch) will be made on the outside of your thigh using clean, sterile tools. Then, a small needle will be used to remove a tiny piece of muscle. This is called a muscle biopsy. This method has not caused bleeding or infections in past participants. There is a chance of numbness or a small scar where the cut is made. In rare cases, the scar could cause pain or a small dent in the muscle that you can see or feel. You will not be allowed to leave until any bleeding has stopped and the area is covered with a clean bandage. We will show you how to care for the area to help prevent infection and bleeding. We use a medicine called lidocaine to numb the

area. There is a small risk of toxicity from this drug, but we use a low dose (0.5%, less than 10–15 ml), which makes this very unlikely. Although having several muscle biopsies means more places where infection could happen, the method we use lowers this risk. When multiple biopsies are done during one visit, extra care will be taken with sterile dressings and bandages to keep the risk of infection as low as possible. Also, because each muscle sample is very small (about 300–400 mg), taking several samples in one visit is not expected to cause more muscle damage or delay healing.

Muscle Sympathetic Nerve Activity (MSNA) risks: The microneurography procedure may involve discomfort when the electrode is inserted through the skin and into the nerve in your leg or arm. This may include a "pins-and-needles" sensation and muscle twitch, which should not last more than 2 minutes. Once the electrode is in place, any discomfort should go away. After the procedure, the leg or arm muscles may feel tired for a day or two. There is also a small risk of temporary "pins-and-needles" sensations or increased sensitivity to touch in the area.

Non-invasive Cardiac Output (NICO):
We will measure your cardiac output (how much blood your heart pumps) using one or both of the following safe and non-invasive methods:

- Finger photoplethysmography: A small cuff is placed on your finger, like a finger blood pressure monitor. It measures blood flow and heart function. There are no known risks with this method.
- Inert gas rebreathing: You will breathe in a special gas mixture from a bag for a short time. This helps us measure how your heart and lungs are working. The main risk is that the bag may not fully match your normal breathing size. If that happens, you can stop the test at any time by removing the mouthpiece and breathing room air.

Both procedures use FDA-approved equipment and are considered safe for human use.

Pregnancy: This study may involve risks to pregnant women or unborn babies that are not known at this time.
If you are able to become pregnant, you will be asked to take a urine pregnancy test at the start of the study. You will also be asked to use an effective form of birth control during the study if you are sexually active.
Examples of acceptable birth control methods include:

- Not having sex (abstinence)
- Birth control pills
- The contraceptive patch or ring
- Condoms

If you become pregnant during the study, you must tell the main researcher or study staff right away. If you do become pregnant, you may be taken out of the study for your safety and the safety of the baby.

Pre-visit Fasting:
You may feel hungrier than usual when you arrive at the lab. This is because you will be asked to fast (not eat or drink anything except water) before your visit. Fasting is important to make sure we get accurate results for your blood tests and blood flow measurements. To help make blood draws easier and more comfortable, you should stay well hydrated by drinking only water before coming to the lab. These procedures have been safely followed

by hundreds of participants, including both healthy individuals and those with medical conditions, without any problems.

Other risks:
Taking part in this study may involve risks that are not yet known. You will be told about any new information that might change your decision to keep participating in the study.

UNFORESEEABLE RISKS
Besides the risks already mentioned, you might experience a new or unknown risk or side effect. If you are pregnant or could become pregnant, taking part in this study might cause risks to the unborn baby that we don't know about yet. If we learn anything new that could affect your decision to stay in the study, we will let you know.

BENEFITS
You may or may not get direct benefits from being in this study. One possible benefit is learning about your physical fitness. The investigators may learn more about how the development of fatigue is influenced by aging.

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
Confidentiality will be maintained by a coded identification system, and all data will be kept by Dr. Markus Amann and the other members of the investigative team. There is the possibility that the University of Utah Institutional Review Board or the VA Medical Center may require access to the data. All data will be stored in a secured area, maintaining confidentiality. 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 in case of research-related injury you can contact: **Dr. Markus Amann (Principal Investigator);** (801) 425-2575 (mobile, 24 hrs./day), Markus.Amann@hsc.utah.edu.

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. 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.

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.

COMPENSATION

Experimental visit 1: $30
Experimental visit 2: $100
Experimental visit 3: $100
Experimental visit 4: $400
Exercise training visits 1-24: total $720 ($30 per session)
Experimental visit 5: $100
Experimental visit 6: $100
Experimental visit 7: $400
Experimental visit 8: $30

You will be compensated an additional $40 for wearing the accelerometer

PRO-RATED COMPENSATION

If participants enroll in the study but are unable to complete a protocol once started, participants will be paid for the visits they have completed, payment will be pro-rated at a rate as outlined above.

COSTS/CO-PAYMENTS

A veteran participant will not be required to pay for care and services (treatment) received as a participants in a VA research project. However, some veterans are required to pay co-payments for medical care and services provided by the VA. These co-payment requirements will continue to apply to medical care and services provided by the VA that are not part of this study.

HOW YOU WILL BE COMPENSATED

Since you will be paid for participating in this study, you will need to complete a direct deposit form through the VA, listing which account you would like us to use to compensate you. The amount you receive for taking part in this study will be turned into the Internal Revenue Service (IRS) as taxable income. You can choose not to provide us with your Social Security Number for this form and still participate in this study, however we will not be able to pay you as outlined in this consent form.

NEW INFORMATION

Sometimes during the course of a research project, new information becomes available about the drugs that are being studied. If this happens, the investigators will tell you about it and discuss with you whether you want to continue in the study.

NUMBER OF PARTICIPANTS

We expect to enroll 60 participants from the VA Salt Lake City Health Care System (VASLCHCS) and the University of Utah.

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. Markus Amann 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.
Your blood samples that are collected for this research study will not include whole genome or whole exome sequencing. This means that the researchers have no plans to look at or try to "read" the protein information that makes up your genes (DNA) from your sample.

Tissue or blood samples obtained from you in this research may help in the development of a commercial product by the Veterans Affairs Medical Center or its research partners. There are no plans to provide financial compensation to you should this occur.

CONSENT

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 participate in this research 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

INTERPRETER STATEMENT: (For Non-English Speaking Participants Only)I confirm that I was present as an interpreter for the duration of the consent process for this research study. I confirm that I am qualified and have the necessary skills to provide interpretation between the participant's language and English. By signing this form, I confirm that I provided a full and complete interpretation of the exchange between the researcher obtaining consent and the participant, to the best of my ability.

_____
Name of Interpreter

_____ _____
Signature of Interpreter Date