Department of Veterans Affairs	Informed Consent Form	COMIRB APPROVED For Use 24-Apr-2019 23-Apr-2020
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Subject Name: _____ **Date:** _____

Title of Study: Cardiovascular Mechanisms of Exercise Intolerance in Diabetes and the Role of Sex

Principal Investigator: Jane Reusch, MD **VAMC:** 554

VA Investigator: Jane Reusch, MD **COMIRB#** 17-0356

You are being asked to be in a research study. This form provides you with information about the study. A member of the research team will describe this study to you and answer all of your questions. Please read the information below and ask questions about anything you don't understand before deciding whether or not to take part.

Why is this study being done?

This study plans to learn more about how Type 2 Diabetes (T2DM) affects the amount of blood and oxygen in your body during exercise.

You are being asked to be in this research study because you are a healthy volunteer or a person with T2DM between the ages of 30 and 55 years.

Up to 120 people will participate in the study.

What happens if I join this study?

If you join the study, you will be asked to visit the University of Colorado Hospital Clinical Translational Research Center (CTRC) for study participation. There will be a total of nine study visits. The total length of the study is expected to be 4 years. Your participation in this study will last for 9 visits over approximately 6-7 months.

Visit 1:

After you sign this consent form, you will be asked to stay for the first visit, which will take 2.5 hours. During this visit the following procedures will be performed:

1. Medical History and Physical Exam: The doctor will do a medical exam on you and will ask you questions about your medical history.
2. Blood Draw: About 4 teaspoons of blood will be taken from a needle placed in your arm.
3. Urinalysis: You will be asked to give a urine sample in a cup.
4. Questionnaires: You will fill out one questionnaire about your exercise habits. You are free to skip any questions you don't want to answer.
5. Pulmonary Function Test (PFT): You will be given a plastic mouthpiece to breathe through. You will be told what kind of breaths to take and for how long.

6. Autonomic Nervous Systems Test (ANS): Ten sensors will be put on the skin of your chest, legs and arms for an electrocardiogram (EKG), which measures your heart rate. You will be told what kind of breaths to take or whether to stand or lay down. You will be given a plastic mouthpiece and you will breathe into it when the doctor tells you.
7. Dietary Counseling: You will meet with a registered dietician for approximately 30 minutes. During this time you will discuss different meal options for the remaining visits, and receive educational materials to increase your knowledge of good food choices.

Visit 2:
This visit will last 2.5 hours. During this visit the following procedures will be performed:

1. Dual-Energy X-ray Absorptiometry (DEXA): You will lie down on a machine called a DEXA scan, which will take pictures of your body like an X-Ray. Although the increased risk to both mother and fetus are small with this radiological exam, a pregnancy test will be done prior to the DEXA, and if you are pregnant or breastfeeding, you will be excluded from this study.
2. Cardiac Echocardiogram (ECHO): An ultrasound of your heart will be done by putting a probe on your chest.
3. Femoral Artery Flow Mediated Dilation (FMD): A probe will be placed on your thigh to do an ultrasound. Then a blood pressure cuff will be placed on your leg and another ultrasound will be taken of your thigh.
4. Graded Exercise Test (GXT): A small plastic sensor will be placed on the skin of your thigh (NIRS). You will sit on a stationary bicycle and exercise while breathing through a plastic mouthpiece. This is called a Graded Exercise Test (GXT). We will ask you to cycle at increasingly harder rates until you tell us you cannot go any harder. The exercise will be stopped if you become uncomfortable in any way, or if you develop an abnormal response to exercise determined by the doctor.
5. A resting and exercise EKG and vital signs will be performed during the visit. An EKG is a non-invasive procedure. Electrodes will be placed on the skin of the chest to measure the electrical activity of the heart. The area of skin where the electrodes are placed may need to be shaved to achieve good contact with the skin.

Visit 3:
This visit will last about 5 hours. During this visit the following procedures will be performed:

1. You will be asked not to eat any food and drink only water from 8pm the night before. You will come into the clinic at 7am.
2. Arterial Stiffness Measurement: Three sensors will be placed on your chest and an ultrasound probe will be placed on your throat, your thigh and your wrist to measure the flexibility and stiffness of your arteries.
3. Muscle Biopsy: The doctor will give you an injection of a numbing medicine on your thigh. A small cut will be made in your thigh and a small piece of muscle will be removed (biopsy). This procedure will be performed on your dominant leg.

4. Insulin Clamp: You will have 2 small plastic tubes (IV) inserted into your arm and your blood will be taken from one tube several times during the day. About 5 ½ ounces of blood in total will be taken. You will be given glucose, insulin, and potassium through the other tube.
5. You will not be able to eat during the visit but will be given a meal to eat at the end of the visit.

Visit 4:
This visit will last about 2 hours. During this visit the following procedures will be performed:

1. Maximum Voluntary Contraction (MVC): You will lie flat on your back with your foot against a pedal. You will be asked to push against the pedal has hard as you can. You will have a chance to try this machine out before the test is done to get used to it
2. Constant work rate/Isometric Exercise Testing: You will lie flat and put one of your feet against a pedal. A small plastic sensor will be placed on the skin of your calf (NIRS) and a sensor will be placed on your finger. You will be asked push and relax your foot against the pedal for a series of exercise bouts. During the exercise a probe, called a Doppler, will be placed on your thigh for a different kind of ultrasound. Two of the exercise bouts will be performed while breathing 100% oxygen.
3. Plethysmography Test: A stretchable wire will be placed around your calf and a blood pressure cuff will be placed on your leg and inflated and deflated several times. To measure how your blood vessels expands the blood pressure cuff will then be inflated for five minutes. When the cuff is released, the blood pressure cuff will be inflated and deflated several times. This will also be done at the end of the last exercise bouts.

Visit 5:
This visit will last about 2 hours. During this visit the following procedures will be performed:

1. Magnetic Resonance Imagining (MRI): You will lie flat in the MRI machine and put one of your feet against a pedal. You will be asked to push and relax your foot against the pedal for a series of exercise bouts. One of the exercise bouts will be performed while breathing 100% oxygen. We will also look at the blood flow through your heart with the MRI machine. You will be asked to relax for the first portion of the test. You will then be asked to perform a series of breath holds for the final portion of the test.

Exercise Training Period:
You will come into the Exercise Research Lab at the CTRC. Training is conducted 3 times a week for 3 months. Exercises are done under the supervision of experienced exercise specialists. Each session will last a total of one hour. You will be asked to wear a heart rate monitor and perform a warm up for 5 minutes, perform 50 minutes of cardiovascular exercise, and then perform a cool-down for 5 minutes. Exercise intensity will be based on your heart rate. You may use a treadmill, stationary bike, elliptical, rowing machine, or a combination of machines. There will also be a 3 week ramp-up period so you can get accustomed to exercising. This is in addition to the 3 month intervention.

Visit 6:
This visit will last 2.5 hours. During this visit the following procedures will be performed:

1. Blood Draw: About 4 teaspoons of blood will be taken from a needle placed in your arm.
2. Urinalysis: You will be asked to give a urine sample in a cup.
3. Cardiac Echocardiogram (ECHO): An ultrasound of your heart will be done by putting a probe on your chest.
4. Femoral Artery Flow Mediated Dilation (FMD): A probe will be placed on your thigh to do an ultrasound. Then a blood pressure cuff will be placed on your leg and another ultrasound will be taken of your thigh.
5. Graded Exercise Test (GXT): A small plastic sensor will be placed on the skin of your thigh (NIRS). You will sit on a stationary bicycle and exercise while breathing through a plastic mouthpiece. This is called a Graded Exercise Test (GXT). We will ask you to cycle at increasingly harder rates until you tell us you cannot go any harder. The exercise will be stopped if you become uncomfortable in any way, or if you develop an abnormal response to exercise determined by the doctor.
6. A resting and exercise EKG and vital signs will be performed during the visit. An EKG is a non-invasive procedure. Electrodes will be placed on the skin of the chest to measure the electrical activity of the heart. The area of skin where the electrodes are placed may need to be shaved to achieve good contact with the skin.

Visit 7:
This visit will last about 5 hours. During this visit the following procedures will be performed:

1. You will be asked not to eat any food and drink only water from 8pm the night before. You will come into the clinic at 7am.
2. Arterial Stiffness Measurement: Three sensors will be placed on your chest and an ultrasound probe will be placed on your throat, your thigh and your wrist to measure the flexibility and stiffness of your arteries.
3. Muscle Biopsy: The doctor will give you an injection of a numbing medicine on your thigh. A small cut will be made in your thigh and a small piece of muscle will be removed (biopsy). This procedure will be performed on your dominant leg.
4. Insulin Clamp: You will have 2 small plastic tubes (IV) inserted into your arm and your blood will be taken from one tube several times during the day. About 5 ½ ounces of blood in total will be taken. You will be given glucose, insulin, and potassium through the other tube.
5. You will not be able to eat during the visit but will be given a meal to eat at the end of the visit.

Visit 8:
This visit will last about 2 hours. During this visit the following procedures will be performed:

1. Maximum Voluntary Contraction (MVC): You will lie flat on your back with your foot against a pedal. You will be asked to push against the pedal has hard as you can. You will have a chance to try this machine out before the test is done to get used to it.

2. Constant work rate/Isometric Exercise Testing: You will lie flat and put one of your feet against a pedal. A small plastic sensor will be placed on the skin of your calf (NIRS) and a sensor will be placed on your finger. You will be asked push and relax your foot against the pedal for a series of exercise bouts. During the exercise a probe, called a Doppler, will be placed on your thigh for a different kind of ultrasound. Two of the exercise bouts will be performed while breathing 100% oxygen.
3. Plethysmography Test: A stretchable wire will be placed around your calf and a blood pressure cuff will be placed on your leg and inflated and deflated several times. To measure how your blood vessels expands the blood pressure cuff will then be inflated for five minutes. When the cuff is released, the blood pressure cuff will be inflated and deflated several times. This will also be done at the end of the last exercise bouts.

Visit 9:

This visit will last about 2 hours. During this visit the following procedures will be performed:

1. Magnetic Resonance Imagining (MRI): You will lie flat in the MRI machine and put one of your feet against a pedal. You will be asked to push and relax your foot against the pedal for a series of exercise bouts. One of the exercise bouts will be performed while breathing 100% oxygen. We will also look at the blood flow through your heart with the MRI machine. You will be asked to relax for the first portion of the test. You will then be asked to perform a series of breath holds for the final portion of the test.

Table of Procedures

	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Exercise Training (3 days/week for 3 months)	Visit 6	Visit 7	Visit 8	Visit 9
Consent/HIPAA	X									
Questionnaires (Activity and Diet Survey)	X									
History and Physical	X									
Blood Draw/ Urinalysis	X						X			
DEXA Scan		X								
ANS testing	X									
Plethysmography				X					X	
Cardiac ECHO		X					X			
Flow Mediated Dilation		X					X			
PFT	X									
Bicycle Graded Exercise Test (GXT)		X					X			
ECG	X	X					X			
NIRS		X		X			X		X	
Maximum Voluntary Contraction Test (MVC)				X					X	
Arterial Stiffness Measurement			X					X		
Insulin Clamp			X					X		
Muscle Biopsy			X					X		
Constant Work Rate Exercise				X					X	
Isometric Exercise				X	X				X	X
Doppler Ultrasound				X					X	
MRI					X					X
Length of Visit (hours)	2.5	2.5	5	2	2		2.5	5	2	2

*Study visits may vary based on your schedule, availability of study equipment, and principle investigator discretion.

What are the possible discomforts or risks?

Any procedure has possible risks and discomforts. The procedures in this study may cause all, some, or none of the risks or side effects listed. Rare, unknown, or unforeseeable (unexpected) risks also may occur.

Discomforts you may experience while in this study include the following:

Leg blood flow using Ultrasound
There may be a slight pressure of the probe against the skin while the measurements are performed.

Blood Draw
In this study we will need to get about 4 teaspoons of blood from you during two visits, and 5 ½ ounces of blood during two visits. We will get blood by putting a needle into one of your veins and letting the blood flow into a glass tube. You may feel some pain when the needle goes into your vein. A day or two later, you may have a small bruise where the needle went under the skin.

IV Risks
In this study we will insert a needle, connected to a plastic tube, into a vein in your arm. We will use the tube to take blood samples or give you fluids. You will feel some pain when we first insert the tube into your vein. You may have some redness, swelling, or bruising where the tube goes under your skin. In some cases, this type of tube can cause an infection where it goes under the skin. In rare cases, it can cause a blood clot in the vein. You will have this tube inserted for up to 5 hours during visits 3 & 7.

Plethysmography/Femoral Artery Diameter (Blood flow measurements)
There may be a slight discomfort while the arm cuff is inflated.

Arterial Stiffness Measurement
There is a very slight chance that fainting or stroke may occur. No actual fainting or stroke has ever been reported. The risk of these happening has been estimated to be less than 1/1,000,000.

General Risks of Exercise during Strength Testing and other Submaximal Exercise
These tests begin with you either seated on a stationary bicycle or lying down on an exercise machine. During certain exercise tests, you will be asked to breathe through a mouth-piece while you exercise. The air that you exhale will be sampled and studied. You will breathe into a mouthpiece connected to a device that measures the amount of oxygen you exhale. Because you are breathing through a mouthpiece, you may sense a slight resistance to breathing. Some additional risks of exercising are sore muscles, fatigue, shortness of breath, chest pain, and lightheadedness. People with diabetes may also experience low blood sugar (hypoglycemia). These risks are identical to the risks associated with the exercise intervention sessions.

Stationary Bicycle Graded Exercise Test (GXT)
Just as during the submaximal exercise test, you will be asked to breathe through a mouthpiece while you exercise and the air you exhale will be sampled and studied. The graded exercise test is a standard clinical procedure, which is routinely performed on hundreds of cardiac subjects every year for diagnosis and evaluation of treatment of their condition. Four in 10,000 people experience abnormal heartbeats or chest pain while doing this test. One in 10,000 people die. Additional risks of exercising are sore muscles, fatigue, shortness of breath, and lightheadedness. People with diabetes may also experience low blood sugar (hypoglycemia). You are not a cardiac patient, so the risks may be overstated.

DEXA scan
As part of this study we will perform one DEXA scan of your entire body. DEXA is a way of looking inside the body by using X-rays. X-rays are a type of radiation. Your natural environment has some radiation in it. This DEXA will give you about the same amount of radiation that you would get from your environment in 2 days.

Insulin Clamp
With the insulin clamp there is the risk of a low blood sugar (hypoglycemia). The symptoms of hypoglycemia are excessive sweating, faintness, headache, pounding heart, trembling, and impaired vision. Under very extreme degrees of hypoglycemia, you may lose consciousness. Your blood sugar will be monitored every 5 minutes and the glucose infusion will be adjusted throughout this test to prevent hypoglycemia from occurring. After the insulin is stopped you will be fed a meal and monitored for another hour to make sure your blood sugar is stable.

Muscle biopsy
In this study we will need to take a small sample of your thigh muscle. This procedure is called a "biopsy". Before we take the samples, we will give you some medication to numb the area. We will then make a small cut in the skin and take the samples by pressing a hollow needle into your muscle. When we take the needle out, it will remove a small circle of muscle called a "plug". There are some risks to taking a sample of muscle this way. There is a chance that you could get an infection where the needles goes in or have some bleeding, bruising, or experience some pain after the procedures. There is also a chance that you could have an allergic reaction to the numbing medicine. After your skin heals up, you will have a small scar from where we take the sample.

MRI
The MRI is a non-invasive scan of your calf muscle using a magnet. There is no radiation and no risk involved with the MRI. The MRI may be loud, therefore the subject is provided with audio protection and optional television to help increase comfort. Some subjects might feel claustrophobic while having an MRI and the scan will be stopped if it cannot be tolerated. In addition, any subjects with implanted metal cannot have an MRI due to the magnet involved.

Echocardiogram
The risks of the echocardiogram (performed for research purposes) are negligible.

There is a risk that people outside of the research team will see your research information. We will do all we can to protect your information, but it cannot be guaranteed.

The study may include risks that are unknown or unforeseeable or unexpected at this time.

Risks of the usual care you receive are not risks of the research and are not included in this consent form. You should talk with your health care providers if you have any questions about the risks of usual care.

What are the possible benefits of the study?

This study is designed for the researcher to learn more about blood flow in type 2 diabetes.

This study is not designed to treat any illness or to improve your health. Also, there may be risks, as discussed in the section describing the discomforts or risks.

Are there alternative treatments?

There may be other ways of treating your type 2 diabetes. Treatments for type 2 diabetes include diet and exercise and/or oral medication. You could also choose to get no treatment at.

You should talk to your doctor about your choices. Make sure you understand all of your choices before you decide to take part in this study. You may leave this study and still have these other choices available to you.

Who is paying for this study?

This research is being paid for by the U.S. Department of Veteran Affairs.

Will I be paid for being in the study?

You will be paid for participation in this study as listed below by study visit.

Visit 1 $25
Visit 2 $75
Visit 3 $150
Visit 4 $50
Visit 5 $50
Exercise Training $150
Visit 6 $75
Visit 7 $150
Visit 8 $50
Visit 9 $50

This will add up to a total of $825 if you complete all of the visits. If you leave the study early, or if we have to take you out of the study, you will be paid only for the visits you have completed.

It is important to know that payments for participation in a study are taxable income. Your SSN will be collected and used to report this taxable income to the IRS.

Will I have to pay for anything?

There will be no cost to you for participation in this study. 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. If you decide to participate in this study, you cannot be charged nor your insurance billed, for research-related interventions or procedures that are required by the protocol.

Is my participation voluntary?

Taking part in this study is voluntary. You have the right to choose not to take part in this study. If you choose to take part, you have the right to stop at any time. If you refuse or decide to withdraw later, you will not lose any benefits or rights to which you are entitled.

If you don't take part or leave this study, you will still receive your normal medical care. The only medical care that you will lose is the medical care you are getting as part of this study. You might be able to get the same kind of medical care outside of the study. Ask your study doctor.

The data and specimens collected prior to withdrawal cannot be withdrawn; however, no further data will be collected.

If you are a VA employee or student, refusal to take part in the study will in no way influence your employment, ratings, subsequent recommendations, or academic progress.

If there are any new findings during the study that may affect whether you want to continue to take part, you will be told about them.

Can I be withdrawn from the study?

The study doctor may decide to stop your participation without your permission, if he or she thinks that being in the study may cause you harm, or for any other reason. Also, the sponsor may stop the study at any time.

What happens if I am injured or hurt during the study?

Every reasonable safety measure will be used to protect your well-being. The Eastern Colorado Health Care System will provide necessary medical care and treatment for any injury that is a result of participation in this study for veterans. Compensation for such an injury may be

permitted by applicable federal laws and/or regulations. The VA is not required to provide treatment for injuries in research studies if the injuries are caused by your non-compliance with study procedures. You should inform your care provider(s) if you decide to participate in this research study. If you have questions about an injury related to the research, call Jane Reusch at 720-723-6342. Study personnel can be reached at any time at 720-848-6688 or 303-266-2477 (pager).

Who do I call if I have questions?

The researcher carrying out this study at the VA is Jane Reusch. You may ask any questions you have now. If you have any questions later you may call Jane Reusch at 720-723-6342. You will be given a copy of this form to keep.

If you have questions regarding your rights as a research subject, concerns or complaints about this research study, please call the Colorado Multiple Institutional Review Board (COMIRB) office at 303-724-1055. This is the Board that is responsible for overseeing the safety of human participants in this study. If you want to verify that this study is approved, please contact the VA Research Office at 720-857-5092. If applicable Information can also be found at http://www.clinicaltrials.gov.

Who will see my research information?

Taking part in this study will involve collecting private information about you. This information includes:

- Name and Demographic Information (age, sex, ethnicity, address, phone number, etc.
- Your social security number
- Portions of your previous and current Medical Records that are relevant to this study, including but not limited to Diagnosis(es), History and Physical, laboratory or tissue studies, radiology studies, procedure results
- Research Visit and Research Test records
- Tissue samples and the data with the samples.

We will keep all research records that contain your identifiable health information, confidential to the extent allowed by law. Records about you will be kept locked in filing cabinets at the VA and on VA computers protected with passwords. Only the research staff will have access to your study information.

We will try to keep your medical records confidential, but it cannot be guaranteed. Records that identify you (including your medical records and the consent form signed by you), may be looked at or portions of your records copied that identify you by others. These include:

- Federal agencies such as the Food and Drug Administration (FDA), the General Accountability Office (GAO), the Office of the Inspector General, Office for Human Research Protections (OHRP), and the Office of Research Oversight (ORO)

that protect research subjects like you, may also copy portions of records about you.

- People at the Colorado Multiple Institution Review Board
- Clinical Translational Research Clinic (CTRC) at the University of Colorado Hospital
- The investigator and research team for this study
- The sponsor (group paying for the study), study monitors or agents for the sponsor
- Officials at the institution where the research is being conducted, and officials at other institutions involved in this study who are in charge of making sure that we follow all of the rules for research
- Our local VA Research and Development Committee
- The University of Colorado, Anschutz Medical Campus, where the research study will take place.

Information about you will be combined with information from other people taking part in the study. We might talk about this research study at meetings. We might also print the results of this research study in relevant journals. But we will always keep the names of the research subjects, like you, private.

A description of this clinical trial will be available on http: http://www.clinicaltrials.gov, as required by U.S. law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

We will ask you to sign a different form that talks about who can see your research records. That form is called a HIPAA Authorization form. It will mention companies and universities who will see your research records.

You have the right to request access to your personal health information from the Investigator. To ensure proper evaluation of test results, your access to these study results may not be allowed until after the study has been completed.

The HIPAA Authorization form that you will also be asked to sign will state when or if it expires. However, you may withdraw this authorization for use and disclosure of your personal health information by providing written request to the Investigator. If you withdraw the HIPAA Authorization form, the Institution, the Investigator, the research staff, and the research Sponsor will no longer be able to use or disclose your personal health information from this study, except so far as that they have already relied on this information to conduct the study.

Is there other information I need to know?

Disclosure of Results: You may request your study procedure results; however, all study procedures are experimental and are being done solely for research purposes.

Re-contact. The researcher would like to store your information (name, birthdate, and contact information) in a research database available to her research lab. This database will be used as a recruitment tool for future studies for type 2 diabetes within her lab. You may change your mind about providing information in the future by informing Dr. Reusch at 720-723-6342.

☐ Yes, I am interested in being contacted to participate in future studies. ____Initials

☐ No, I am not interested in being contacted to participate in future studies. ____Initials

Agreement to be in this study

I have read this form or it has been read to me. A member of the research team has explained the study to me and answered my questions. I have been told about the risks or discomforts and possible benefits of the study. I have been told of other choices of treatment available to me.

I have been told that I do not have to take part in this study. 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 my records will not be revealed unless required by law.

In case there are medical problems or questions, I have been told I can call Jane Reusch, MD at 720-723-6342 during the day and at 303-266-2006 after hours. If any medical problems occur in connection with this study, the VA will provide the necessary medical care.

I choose to participate in this study. A copy of this consent form will be placed in my medical record.

Subject's Signature: _____ Date:_____

Print name: _____

Consent form explained by: _____ Date: _____

Print name: _____

Investigator: _____ Date: _____

Print name: _____

If this consent form is read to the subject because the subject is unable to read the form, an impartial witness not affiliated with the research or investigator must be present for the consent, must sign the following statement, and check the appropriate box:

Witness Signature: _____ Date: _____

Print Name: _____

Witness of Signature ☐

Witness of Consent Process ☐