CONSENT FORM TO PARTICIPATE IN A RESEARCH STUDY

INVESTIGATOR'S NAME: JAUME PADILLA, PHD
PROJECT IRB #: 2008181
STUDY TITLE: RESTORING VASODILATOR ACTIONS OF INSULIN: EFFECTS OF AN ACUTE BOUT OF LEG HEATING

INTRODUCTION

This consent may contain words that you do not understand. Please ask the investigator or the study staff to explain any words or information that you do not clearly understand.

This is a research study. Research studies include only people who choose to take part. Before participating in a research study, you have the right to know about the study expectations and tests that will be used in this study. This will allow you to make a choice on whether or not to join. The information presented here is simply an effort to make you better informed so that you can make your choice of whether or not to join this research study.

This is a clinical trial and a description of this clinical trial is available on www.ClinicalTrials.gov (#NCT03203694), as required by U.S. law. This web site does not include information that can identify you. At most, the web site includes a summary of the results. You can search this web site at any time.

Please take your time to make your decision and discuss it with your family and friends.

You are being asked to take part in this study because you are between the ages of 18 and 65.

This study is being sponsored by the University of Missouri, Department of Nutrition and Exercise Physiology.

In order to participate in this study, it will be necessary to give your written consent.

WHY IS THIS STUDY BEING DONE?

The purpose of the present study is to determine the effects of a single bout of leg heating on leg vascular adaptations.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?

About 20 people will take part in this study at the University of Missouri.

WHAT IS INVOLVED IN THE STUDY?

You will initially be screened to see if you meet the criteria of the study.

Experimental Visit: Prior to participating in the study, you will provide written informed consent. If you take part in this study, you will arrive at 7am to the University Hospital Clinical Research Center (CRC) after an overnight fast, having not taken medications, and not exercised for 24-48hrs. Basic measures, including medical history and physical activity questionnaire, body weight, height, and waist circumference will be taken. You will then undergo single leg heating for one hour. The other leg will serve as the internal control and not be heated. Leg assignment will be randomized by flipping a coin. Leg heating will be accomplished via water bath immersion at a temperature of 40-42°C (104-107 F), using a custom-made temperature-controlled water bath. During leg heating, you will be seated and water

will reach the level below the knee. The purpose of leg heating is to increase leg blood flow. This water temperature is below the threshold for pain sensation or burning.
After heating the leg, blood flow measurements before and during the insulin clamp will be performed, as described below.

Blood flow measures: We will measure the blood flow to your leg by placing an ultrasound probe over the popliteal artery (lower leg artery). The probe will provide a measure of the speed at which your blood is traveling through your artery and the extent to which your artery dilates (i.e., expands). A pressure sensor (tonomter, the size of a pencil) will be placed over the skin of the neck region to obtain the pressure wave form in the carotid artery. Additionally, in order to further characterize muscle blood flow, we will be using an ultrasound to image the muscle of your leg during the administration of an ultrasound contrast agent that will be given through the IV. This agent, called Definity, is composed of tiny microbubbles smaller than the size of a red blood cell. These bubbles stay inside the blood vessels and go where the red blood cells go. This contrast agent allows us to evaluate blood flow in your leg muscle. Definity has been FDA approved for use in humans during ultrasound of the heart cavity and has been shown to be safe.

Insulin clamp: The insulin clamp test helps to determine how well your body disposes of blood sugar (glucose) in response to insulin. You will have a small catheter (tube) placed into a vein in both of your arms. The insulin clamp requires that insulin and glucose be slowly infused into the arm vein and then multiple small blood samples will be taken during a 3 hour period allowing us to accurately assess your insulin sensitivity. During the entire test you will lay comfortably in a bed. The total volume of blood drawn per insulin clamp will be less than 120mL (~25 teaspoons). During this time, we will perform repeated measures of blood flow in both legs and leg muscle blood flow using the ultrasound probe, measures of blood pressure, and measures of heart rate via ECG.

This visit will last approximately 6 hours.

HOW LONG WILL I BE IN THE STUDY?
You will be in the study for one visit. You can stop participating at any time. Your decision to withdraw from the study will not affect in any way your medical care and/or benefits.

WHAT ARE THE RISKS OF THE STUDY?
While on the study, you are at risk for the side effects described below. You should discuss these with the investigator and/or your doctor. There may also be other side effects that we cannot predict. Risks and side effects related to the procedures in this study include:

Leg heating: There are no risks associated with this intervention. The lower leg will be submerged into a temperature-controlled water bath that is set at 40-42°C (104-107 F). This water temperature is well below the threshold for pain sensation or burning. Temperature of the water will be continuously monitored.

Insertion of venous catheters: The potential risks of venous catheterization include infection, swelling and discomfort at the catheter insertion sites. Some bleeding may occur during the insertion of the catheters as well after the catheters have been removed. There is also the possibility of fainting, dizziness, and possible pain and bruising as a result of catheter insertion. These risks will be greatly minimized by using sterile procedures and having an experienced registered nurse placing the venous catheters.

Insulin clamp: The potential risks during the clamp include mild nausea or light-headedness, and mild to moderately high or low blood glucose levels. However, blood glucose will be continually monitored throughout the test. Also, drinks and snacks will be available at the completion of testing should you have low blood sugar or feel nauseous.

Perflutren (Definity): A potential side effect from the perflutren ultrasound contrast agents is temporary back pain, joint pain, headache, shortness of breath, or flushing. These symptoms occur in about one in 200 subjects and are mild in intensity in 90% of those who experience this reaction. If this happens then let us know and infusion of the agent will be stopped. The back and joint pain will go away in a few minutes. A serious allergic reaction to ultrasound contrast agents is unlikely (1 in 10,000), but possible. Symptoms of an allergic reaction include: Rash, itching, swelling, severe dizziness, chest pain and trouble breathing. We are using this contrast agent to measure blood flow in your leg muscles using a dose approved by the FDA.

Heart rate measurements via ECG: Some people may have a skin irritation from the patches that connect the wires on your chest to the computer. Skin and hair are pulled slightly when the patches are removed after the test. Research personnel will attach and remove the patches as carefully as possible.

Drugs:

Insulin**:** Insulin will be administered through the vein catheter to increase circulating levels of insulin during the clamp. The potential side effects of insulin infusion may include mild nausea or light-headedness as a result of too low levels of blood sugar. To ensure this does not occur, blood sugar will be checked throughout the clamp. In addition, dextrose (sugar) will be simultaneously administered to maintain constant levels of blood sugar. After completion of the insulin clamp, you will be given snacks if needed.

Dextrose: Dextrose is a sugar that will be administered through the vein catheter to maintain your levels of blood sugar constant throughout the clamp. Administration of fluid may increase the urge to urinate. A portable urinal and privacy will be made available if needed.

Perflutren (Definity): Contrast agent used in contrast enhanced ultrasound procedure. Definity will be infused IV utilizing a syringe pump at a rate of 2mL/min immediately prior to ultrasound imaging of the leg muscle.

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

If you agree to take part in this study, there may or may not be direct medical benefit to you. You may expect to benefit from taking part in this research to the extent that you are contributing to medical knowledge. Indeed, we hope the information learned from this study will lead to future strategies to combat cardiovascular disease. You may benefit from the proposed study by learning more about your cardiovascular and metabolic health. In addition, you may also benefit from the leg heating intervention designed to improve vascular function.

WHAT OTHER OPTIONS ARE THERE?

An alternative is to not participate in this research study. At any point, you can change your mind about being in the study.

WHAT ABOUT CONFIDENTIALITY?
Information produced by this study will be stored in the investigator's file and identified by a code number only. The code key connecting your name to specific information about you will be kept in a separate, secure location. Information contained in your records may not be given to anyone unaffiliated with the study in a form that could identify you without your written consent, except as required by law. It is possible that your medical and/or research record, including sensitive information and/or identifying information, may be inspected and/or copied by the study sponsor (and/or its agent), the Food and Drug Administration (FDA), federal or state government agencies, or hospital accrediting agencies, in the course of carrying out their duties. If your record is inspected or copied by the study sponsor (and/or its agents), or by any of these agencies, the University of Missouri will use reasonable efforts to protect your privacy and the confidentiality of your medical information.

The results of this study may be published in a medical book or journal or used for teaching purposes. However, your name or other identifying information will not be used in any publication or teaching materials without your specific permission.

WHAT ARE THE COSTS?
You will not be charged for any of the tests or procedures done for the research study. You will be responsible for your travel to and from the laboratory/testing facilities.

WILL I BE PAID FOR PARTICIPATING IN THE STUDY?
You will be compensated $100 for completion of the duration of the study. If you discontinue the study, you will be compensated $10 for every hour spent in the laboratory/testing facility.

The method of payment will be check.

WHAT IF I AM INJURED?
It is not the policy of the University of Missouri to compensate human subjects in the event the research results in injury. The University of Missouri, in fulfilling its public responsibility, has provided medical, professional and general liability insurance coverage for any injury in the event such injury is caused by the negligence of the University of Missouri, its faculty and staff. The University of Missouri also will provide, within the limitations of the laws of the State of Missouri, facilities and medical attention to subjects who suffer injuries while participating in the research projects of the University of Missouri. In the event you have suffered injury as the result of participation in this research program, you are to contact the Risk Management Officer, telephone number (573) 882-1181, at the Health Sciences Center, who can review the matter and provide further information. This statement is not to be construed as an admission of liability.

WHAT ARE MY RIGHTS AS A PARTICIPANT?

Participation in this study is voluntary. You do not have to participate in this study. Your present or future care will not be affected should you choose not to participate. If you decide to participate,

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you can change your mind and drop out of the study at any time without affecting your present or future care in the University of Missouri Health Care System. Leaving the study will not result in any penalty or loss of benefits to which you are entitled. In addition, the investigator of this study may decide to end your participation in this study at any time after he/she has explained the reasons for doing so and has helped arrange for your continued care by your own doctor, if needed.

You will be informed of any significant new findings discovered during the course of this study that might influence your health, welfare, or willingness to continue participation in this study.

WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?
If you have any questions regarding your rights as a participant in this research and/or concerns about the study, or if you feel under any pressure to enroll or to continue to participate in this study, you may contact the University of Missouri Health Sciences Institutional Review Board (which is a group of people who review the research studies to protect participants' rights) at (573) 882-3181.

You may ask more questions about the study at any time. For questions about the study or a research-related injury, contact Dr. Jaume Padilla at padillaja@missouri.edu or (812) 345-3566

A copy of this consent form will be given to you to keep.

I authorize the investigators to keep this information and any information from my participation in their studies in a database so that they may contact me regarding future studies.

YES _____ NO _____

SIGNATURE
I confirm that the purpose of the research, the study procedures, the possible risks and discomforts as well as potential benefits that I may experience have been explained to me. Alternatives to my participation in the study also have been discussed. I have read this consent form and my questions have been answered. My signature below indicates my willingness to participate in this study.

_____ _____
Subject/Patient Date

_____ _____
Witness Date

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SIGNATURE OF STUDY REPRESENTATIVE

I have explained the purpose of the research, the study procedures, identifying those that are investigational, the possible risks and discomforts as well as potential benefits and have answered questions regarding the study to the best of my ability.

_____ _____

Study Representative**** Date

****Study Representative is a person authorized to obtain consent. Per the policies of the University of Missouri Health Care, for any 'significant risk/treatment' study, the Study Representative must be a physician who is either the Principal or Co-Investigator. If the study is deemed either 'significant risk/non-treatment' or 'minimal risk,' the Study Representative may be a non-physician study investigator.

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