CONSENT FOR RESEARCH
Penn State College of Medicine
The Milton S. Hershey Medical Center

Title of Project: Effects of heating on exercise pressor reflex in peripheral artery disease: Exercise ability

Principal Investigator: Jian Cui, PhD

Address: Heart and Vascular Institute
500 University Drive
Hershey, PA 17033

Telephone Numbers: Weekdays: 8:00 a.m. to 5:00 p.m. (717) 531-4589.
After hours call (717) 531-8521. Ask for the Cardiology doctor on 24-hour call.

Subject's Printed Name: _____

We are asking you to be in a research study.

Whether or not you take part is up to you. You can choose not to take part. You can agree to take part and later change your mind. Your decision will not be held against you.

This form gives you information about the research. Please ask questions about anything that is unclear to you and take your time to make your choice.

1. Why is this research study being done?

We are asking you to be in this research because you have been diagnosed with Peripheral arterial disease (PAD) or you are a healthy volunteer.

This research is being done to find out whether a heat exposure (e.g. a warm bath) will improve the exercise ability in PAD patients.

Approximately 39 people will be take part in this research study at the Hershey Medical Center.

2. What will happen in this research study?

This study may involve up to 5-6 visits per person. The Screening visit may be combined with the first testing visit or may be on a separate day. You do not have to participate in all of the visits, but we hope you will consider it. The order of testing visits may be different between subjects.

Before you arrived today, you were asked to refrain from caffeine for 12 hours; and refrain from alcohol, recreational and/or medicinal marijuana, over the counter medications, and extreme exercise for 24 hours before the visit. PAD patients were asked to take the medications according to their regular schedule but at a similar time on the days of these visits.

Screening visit and Visit 1: Walking ability without heat treatment

You will report to the Clinical Research Center (CRC) and one of our research nurses will explain the study to you, answer all your questions, and have you sign this consent form. A brief medical history and physical examination will be performed by licensed medical personnel to help determine your eligibility to continue in this study. If you are a woman of childbearing potential, a urine pregnancy test will be performed at the beginning of *each visit* to ensure that you are not pregnant. If you are pregnant, you will be withdrawn from the study. If you are a PAD patient or a healthy volunteer, a resting 12-lead EKG may be performed by licensed medical personnel.

You will be positioned comfortably on the bed and your Ankle/Brachial Index (ABI) will be determined on both sides of your body by measuring the blood pressure in both your left and right ankles and arms. The ankle-brachial index test compares your blood pressure measured at your ankle with your blood pressure measured at your arm and

is used to check for PAD. If after completion of these screening activities, the investigators determine that you meet the enrollment criteria to continue in this study, you will be invited to participate in Visit 1 activities.

A round disk holding several small probes will be taped to your skin and moved between several locations on your arms and legs to measure skin blood flow and skin temperature. To ensure that the disk will be placed on the exact same positions during a later measurement, the position of the disk will be marked with a pen. Photos of the disk placement only may be taken to ensure proper placement during a later measurement. Then, the disk will be removed and a Gardner treadmill protocol will be performed to determine your walking time. Treadmill testing is an important assessment method for doctors to evaluate walking ability in patients with PAD. Adhesive patches (EKG pads) will be placed on your chest to measure your heart rate, and a cuff on your arm and finger to continuously monitor blood pressure. Two plastic sensors will be attached to your lower leg. These sensors use Near Infrared Spectroscopy (NIRS) to non-invasively measure oxygen content in your calf muscles. You will walk on a treadmill that begins at 2 miles/hour and 0% incline for 2 minutes. The grade will increase by 2% every 2 minutes (the speed remains 2 mph) until you say you are too tired to continue walking or a maximum of 22 minutes. After the treadmill test is over, the disk containing the small probes will be placed on the marked sites to repeat the measurements of skin blood flow and skin temperature. Then, the instrumentation will be removed and you may leave.

Visit 2: Walking ability after a warm bath.

You will change into your swimming suit and then be asked to swallow a temperature pill (the size of a large vitamin pill) to measure the temperature from your stomach/intestines and transmit that information to a device outside your body. If you have a pacemaker or other device(s) in your body, you will not swallow the temperature pill, but will have a metal tab placed under your tongue to measure your internal temperature instead. Your body temperature will also be measured every 3 minutes using a tympanic (ear) or temporal (forehead) thermometer.

We will record your blood pressure and heart rate, skin blood flow and skin temperature, at rest before the warm bath. Then you will sit in a bathtub with water up to your shoulders, while one arm will be elevated out of water for skin temperature, blood pressure and heart rate measurements. A cuff on your arm and finger will be placed to monitor blood pressure. These measurements along with water temperature will be monitored and recorded continuously throughout the bath. The initial water temperature will start at about 102.2-104°F (39-40°C). After you get into the bathtub, warm water will be gradually mixed in the tub until it reaches 105.8^{o}F (41°C). During the bath, the water temperature will be maintained by mixing in more warm water when necessary. If you feel the water is getting too hot for you, the heating process will be stopped even if the temperature is below 105.8^{o}F (41°C). Then, until the end of the bath, the water temperature will remain at that temperature. The total bath duration will be about 30 minutes.

After the end of the bath, you will be transported in a wheelchair from the HMC personal care room to the laboratory in the CRC. The use of the wheelchair is to reduce any possible influence of walking on the results of the following protocol. Approximately 40-60 minutes after the end of the bath, the ABI, skin blood flow, skin temperature and Gardner treadmill protocol from Visit 1 will be repeated.

Visit 3: Walking ability after a neutral temperature bath.

The procedure and measurements for the neutral temperature bath will be similar with the warm bath described in Visit 2. However, the water temperature for the bath will be maintained at about 95-98.6^{o}F (35-37°C). After the end of the bath, you will be transported in a wheelchair from the HMC personal care room to the laboratory in the CRC. Approximately 40-60 minutes after the end of the bath, the ABI's, skin blood flow, skin temperature, and Gardner treadmill protocol described in Visit 1 will be repeated.

Visit 4: Walking ability after whole body heating with suit.

You will again be asked to swallow a temperature pill or the metal tab may be placed under your tongue to measure your internal temperature instead. Your body temperature will be also measured every 3 minutes using a tympanic (ear) or temporal (forehead) thermometer.

Small metal tabs will be taped on your skin (chest, abdomen, upper back, lower back, thigh and calf) to measure your skin temperature.

You will put on a special suit that covers your body, arms and legs. This suit is worn on top of your shorts and t-

shirt and has many small water tubes that run through the suit's material but the water does not contact your skin.

You will lie on a table and the following instrumentation will be place on you.

- Patch electrodes for continuous monitoring of EKG.
- A cuff on your arm and finger will continuously monitor blood pressure.
- A stretchy belt will monitor your breathing.
- Small probes will be taped on your skin (4 limbs) to measure skin blood flow. Another small probe be taped on your skin to measure sweat.
- A probe may be placed on your chest to painlessly measure heart function and/or blood flow

Whole-body heating will be accomplished by circulating warm water (about 113 – 122 ^{o}F or 45 – 50 ^{o}C) through the plastic tubes in the special suit until your average skin temperature reaches 100°F (38°C). You will feel comfortable at the beginning of heating (about 20 minutes) and may feel warm during the later period. Whole body heating will continue until the increase in your internal body temperature reaches the level seen during the warm bath in Visit 2. Then, the heating will be stopped.

Approximately 40-60 minutes after the end of the heating, the ABI's, skin blood flow, skin temperature and Gardner treadmill protocol in Visit 1 will be repeated.

Visit 5: Walking ability after lower limbs warm water immersion.

All measurements for the warm bath described in Visit 2 will be also performed during this visit. In addition, your skin temperature and skin blood flow (e.g. on a thigh and/or forearm) will be also measured. You will sit on a chair and put your lower legs and feet in a bucket with warm water for 30 minutes. The water level will be just below your knees. The water temperature will be monitored and controlled at ~ 100 - 108 °F (38 - 42 °C) throughout the 30 minutes. Approximately 40-60 minutes after the end of the leg water immersion, the ABI's, skin blood flow, skin temperature, and Gardner treadmill protocol described in Visit 1 will be repeated.

Visit 6: Walking ability after 1 leg warm water immersion.

If you are willing to return for another visit, you may be asked to return to repeat Visit 5 during which you put only one leg and the foot in the warm water bath.

Order of Study Visits: The order of the visits may be changed and some of the procedures may be eliminated due to time constraints or subject comfort. You may be asked to return for a repeat visit if the data was not usable data or could not be obtained for some reason.

3. What are the risks and possible discomforts from being in this research study?

There is a risk of loss of confidentiality if someone other than the investigators obtains your information or your identity, but precautions will be taken to prevent this from happening. The confidentiality of your electronic data created by you or by the researchers will be maintained to the degree permitted by the technology used. Absolute confidentiality cannot be guaranteed.

It is important that a fetus not be exposed to any unnecessary risks; therefore pregnant women will not be studied. A urine pregnancy test will be administered at the beginning of each visit to all women of childbearing potential to ensure that they are not pregnant.

There are no risks to refraining from caffeine, alcohol, recreational and or medicinal marijuana or exercise before a visit.

The risk of holding over-the-counter medication would be pain, if you are holding pain medication, or allergy symptoms if you are holding allergy medication. If there are any concerns about holding over-the-counter medications, we will discuss them with the study physician.

There is no risk or discomfort associated with the measurements of blood pressure, heart rate, breathing, skin temperatures, sweat rate, oxygen in the muscle (NIRS), or skin blood flow. EKG pads may irritate the skin.

You should excrete the telemetry pill within 24-72 hours, and it is advised that you do not have any MRI (Magnetic Resonance Imaging) procedures within 72 hours of swallowing this pill due to the metal contained in it. The size of the telemetry pill is similar to a large vitamin pill. If you have a pacemaker or have trouble swallowing the pill, your internal temperature will be measured continually with the metal tab placed under your tongue and also measured every 3 minutes using a tympanic thermometer in your ear.

Treadmill walking using Gardner protocol has a minimal risk of temporary lightheadedness, fainting, chest discomfort, leg cramps, occasional irregular heartbeats, shortness of breath or abnormal blood pressure response.

Whole body heating will increase body temperature, sweating, and heart rate. Blood pressure may drop slightly in some subjects during heating. The warm bath or whole body heating will be terminated if your internal temperature exceeds 103°F (39.5°C). Temperatures below this level are well tolerated and have no risk. There are no additional risks or discomforts from the lower limb immersion bath.

You will be monitored continuously for adverse effects and the medical personnel will remain in the room during the study.

4. What are the possible benefits from being in this research study?

4a. What are the possible benefits to me?

You will not benefit from this research study.

4b. What are the possible benefits to others?

Medical science may gain further understanding of nervous system responses in patients with PAD compared with healthy people.

5. What other options are available instead of being in this research study?

You may choose not to be in this research study.

6. How long will I take part in this research study?

If you agree to take part in this research, it may take approximately 1-2 months to complete all of the research visits. Each of the 5-6 research visits will take about 2-3 hours. You may also be asked to return for additional research visits if there was a problem collecting data.

7. How will you protect my privacy and confidentiality if I decide to take part in this research study?

7a. What happens to the information collected for the research?

Efforts will be made to limit the use and sharing of your personal research information. In our research files at The Milton S. Hershey Medical Center (HMC) and Penn State College of Medicine (PSU) we will include these identifiers (name, address, phone number, email address, social security number, date of birth, and medical record number).

A list that matches your name with your code number will be kept in a secure, password protected computer program called Redcap.

Your research records will be labeled with your code number and will be kept in a separate secure, password protected computer file on an IT maintained Penn State Hershey Medical Center computer of the PI or his designate on the research team.

This research is covered by a Certificate of Confidentiality from the National Institutes of Health. This means that the researchers cannot disclose information that identifies you to anyone not connected with the research. This protection also prevents this information from being used or disclosed for legal proceedings, such as being accessed through a court order. The Certificate of Confidentiality however does not prevent disclosures required by law, such as information about child abuse or neglect and harm to yourself or others. Also, your information may be disclosed in accordance with any consent you provide, including for your medical treatment or use in other research. Additionally, the Certificate of Confidentiality does not prevent your information from being disclosed to NIH in order for it to evaluate or audit the research, or prevent disclosures required to meet FDA requirements. For additional information ask the principal investigator or a member of the study team or contact the Human Subjects Protection Office at (717) 531-5687.

In the event of any publication or presentation resulting from the research, no personally identifiable information will be shared.

7b. How will my identifiable health information be used?

If you give your consent, health information that can be traced to you will be collected for this research study. In general, under federal law, health information is private. However, there are exceptions to this rule, and you should know who may be able to see, use, and share your health information for research and why they may need to do so. We will use and disclose your information only as described in this form and in the HMC Privacy Notice.

The research team may use the following health information:

- Past, present, and future medical records
- New health information from tests, procedures, visits, interviews, or forms filled out as part of this research study.

The following people/groups may see, use, and share your identifiable health information:

- HMC/PSU research staff involved in this study
- The HMC/PSU Institutional Review Board (IRB), a group of people who review the research study to protect subjects' rights and welfare
- The HMC/PSU Human Subjects Protection Office
- The HMC/PSU Research Quality Assurance Office
- Non-research staff within HMC/PSU who need this information to do their jobs (such as for treatment, payment (billing), or health care operations)
- Federal and state agencies (such as the U.S. Food and Drug Administration, the Office for Human Research Protections, the Department of Health and Human Services, the National Institutes of Health, and other U.S. or foreign government bodies that oversee or review research)
- People or groups that we hire to do work for us, such as data storage companies, insurers, and lawyers
- A group that oversees the data (study information) and safety of this research
- Organizations that provide independent accreditation and oversight of hospitals and research

These groups may also review and/or copy your original PSU/HMC records while looking at the results of the research study. It is possible that some of the other people/groups who receive your health information may not be required by Federal privacy laws to protect your information. We share your information only when we must, and we ask anyone who receives it from us to protect your privacy.

Because research is an ongoing process, your permission for the use, storage and sharing of your health information will continue indefinitely.

Your privacy rights:

- You have the right to refuse to sign this form that allows us to use and share your health information for research; however, if you don't sign it, you will not be able to take part in this research study.
- You have the right to withdraw your permission for us to use or share your health information for this research study. If you want to withdraw your permission, you must notify the person in charge of this research study in writing using the address on the front of this form. Once permission is withdrawn, you cannot continue to take part in the study.
- If you withdraw your permission, we will stop collecting health information about you for this study; we may continue to use and share your health information that we already have if it is necessary for safety and scientific soundness of the research study; and we will not be able to take back information that has already been used or shared with others.
- You have the right to see and get a copy of your health information that is used or shared for treatment or for payment. However, you may not be allowed to see or copy certain health information that is a part of this research study. This is only for the period of the study. You will be allowed to see that information when the entire research study is complete.

8. What are the costs of taking part in this research study?

8a. What will I have to pay for if I take part in this research study?

There is no cost to you for taking part in this study.

8b. What happens if I am injured as a result of taking part in this research study?

It is possible that you could develop complications or injuries as a result of being in this research study. If you experience a side effect or injury and emergency medical treatment is required, seek treatment immediately at any medical facility. If you experience a side effect or injury and you believe that emergency treatment is not necessary, you should contact the principal investigator listed on the first page of this consent form as soon as possible and the principal investigator will arrange for medical treatment.

HMC/PSU compensation for injury

- There are no plans for HMC/PSU to provide financial compensation or free medical treatment for research-related injury.
- If an injury occurs, medical treatment is available at the usual charge.
- Costs will be charged to your insurance carrier or to you.
- Some insurance companies may not cover costs associated with research injuries.
- If these costs are not covered by your insurance, they will be your responsibility.

When you sign this form you are not giving up any legal right to seek compensation for injury.

9. Will I be paid to take part in this research study?

You will receive $25/hour for your participation in this research study. If you do not complete the study for any reason, you will be paid for the visits you have completed. The payment will be provided by Greenphire Clincard.

This reimbursement will be issued by an external company called Greenphire, which will issue your reimbursement. You will be issued a ClinCard, which is a debit card that your funds are loaded onto and can be used at your discretion. The research team will give Greenphire some personal information about you, as described below. Greenphire will only use your personal information to process this reimbursement and will not share it with anyone for any other purpose. Details of the debit card system are explained on an additional sheet. If you lose the card, you may be responsible for the replacement fee.

When a visit is completed, funds will be approved and loaded onto your card. The funds will be available within 2-3 business days. In order to assign a ClinCard to you and load funds onto the ClinCard, Greenphire will need your Study/Subject ID, Name, Address, date of birth and Social Security Number.

You will have the option to receive updates related to payment alerts via text message and/or email message. Standard text messaging rates will apply. In order to send you messages Greenphire will need your Mobile Phone Number and/or E-mail Address

Payment received as compensation for participation in research is considered taxable income. If payments from Greenphire exceed $600 in any one calendar year, Greenphire will file a 1099 (Miscellaneous Income) form on behalf of Penn State.

10. Who is paying for this research study?

The institution and investigators are receiving a grant from National Institutes of Health to support this research.

11. What are my rights if I take part in this research study?

Taking part in this research study is voluntary.

- You do not have to be in this research.
- If you choose to be in this research, you have the right to stop at any time.

- If you decide not to be in this research or if you decide to stop at a later date, there will be no penalty or loss of benefits to which you are entitled

During the course of the research you will be provided with any new information that may affect your health, welfare or your decision to continue participating in this research.

12. If I have questions or concerns about this research study, whom should I call?

Please call the head of the research study (principal investigator), Jian Cui at 717-531-1799 or 6853, or the Cardiology doctor on 24-hour call at 717-531-8521 if you:

- Have questions, complaints or concerns about the research.
- Believe you may have been harmed by being in the research study.

You may also contact the research protection advocate in the HMC Human Subjects Protection Office (HSPO) at 717-531-5687 if you:

- Have questions regarding your rights as a person in a research study.
- Have concerns or general questions about the research.
- Have questions about your privacy and the use of your personal health information.
- You may also call this number if you cannot reach the research team or wish to offer input or to talk to someone else about any concerns related to the research.

You may visit the HSPO's website at http://pennstatehershey.org/irb under research subject information for:

- Information about your rights when you are in a research study;
- Information about the Institutional Review Board (IRB), a group of people who review the research to protect your rights; and
- Links to the federal regulations and information about the protection of people who are in research studies. If you do not have access to the internet, copies of these federal regulations are available by calling the HSPO at (717) 531-5687.

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

INFORMED CONSENT AND AUTHORIZATION TO TAKE PART IN RESEARCH

Signature of Person Obtaining Informed Consent

Your signature below means that you have explained the research to the subject or subject representative and have answered any questions he/she has about the research.

_____	_____	_____	_____
Signature of person who explained this research	Date	Time	Printed Name

(Only approved investigators for this research may explain the research and obtain informed consent.)

Signature of Person Giving Informed Consent and Authorization

Before making the decision about being in this research you should have:

- Discussed this research study with an investigator,
- Read the information in this form, and
- Had the opportunity to ask any questions you may have.

Your signature below means that you have received this information, have asked the questions you currently have about the research and those questions have been answered. You will receive a copy of the signed and dated form to keep for future reference.

Signature of Subject

By signing this consent form, you indicate that you voluntarily choose to be in this research and agree to allow your information to be used and shared as described above.

_____	_____	_____	_____
Signature of Subject	Date	Time	Printed Name