UNIVERSITY OF OREGON

Consent for Research Participation

Title:	Histamine as a Molecular Transducer of Adaptation to Exercise (Aim 1a)
Sponsor:	NIH
Researcher(s):	John R Halliwill, Ph.D. and colleagues, University of Oregon
Researcher Contact Info:	541-346-7591 halliwil@uoregon.edu

You are being asked to participate in a research study. The box below highlights key information about this research for you to consider when making a decision whether or not to participate. Carefully consider this information and the more detailed information provided below the box. Please ask questions about any of the information you do not understand before you decide whether to participate.

Key Information for You to Consider

- **Voluntary Consent**. You are being asked to volunteer for a research study. It is up to you whether you choose to participate or not. There will be no penalty or loss of benefits to which you are otherwise entitled if you choose not to participate or discontinue participation.
- **Purpose**. The purpose of this research is to determine if heat is a possible stimulus for the release of histamine from mast cells during exercise.
- **Duration.** It is expected that your participation will last 7 hours over 2 days.
- **Procedures and Activities.** You will be asked to undergo single limb heating and a variety of clinical tests including a blood draw and the infusion of two drugs through microdialysis. One of these drugs is experimental.
- **Risks.** Some of the foreseeable risks or discomforts of your participation include heat related discomfort, muscle soreness, allergic reaction to drug infusions, and infection at site of blood collection or thermocouple and microdialysis probe placement.
- **Benefits**. No direct benefit but the researchers hope to learn what causes blood flow increases to occur after exercise.
- **Alternatives.** Participation is voluntary and the only alternative is to not participate.

Why is this research being done?

When humans exercise, there is an increase in blood flow to the skeletal muscle. This increase in blood flow lasts for several hours after exercise as a result of vasodilation in the blood vessels (increasing the diameter of blood vessels). Previous studies have shown that this vasodilation is largely the result of a release of histamine. Histamine is released from mast cells, but the stimulus that activates this release of histamine from mast cells is still debated.

The purpose of the research is to determine if heat is a possible stimulus for the release of histamine from mast cells during exercise. This protocol will explore the changes in temperature of both muscle and skin with external heating of the leg to simulate what happens during exercise. This topic is both clinically and scientifically important. As such, this study is currently funded by the National Institutes of Health. You are being asked to participate because you are a young healthy individual, who is either sedentary, recreationally active, or a trained athlete and free from any known cardiovascular disease. About 48 people will take part in this research.

How long will I be in this research?

We expect that your participation will last 7 hours over 2 days (one screening visit and one study visit). The first visit will last one hour. The study visit will last six hours.

What happens if I agree to participate in this research?

If you agree to be in this research, your participation will include a screening visit and a study visit.

Screening Visit

You will arrive at Dr. Halliwill's laboratory at the Bowerman Sports Science Center at Hayward Field at the University of Oregon for a screening visit. This screening visit will take approximately one hour. You will meet with one of the investigators of the study to discuss the project, to see the laboratory, and to read this form. To determine if you fit the inclusion criteria for the study, you will be asked questions about your health history, you will be given a physical activity questionnaire which will allow investigators to determine your activity level, and your height, weight, and resting blood pressure will be measured. You will also undergo Doppler ultrasonography of your thigh (vastus lateralis muscle). A small probe (ultrasound Doppler probe) will be held on your thigh to image the muscle. The probe uses ultrasound waves to identify tissues in the leg. This allows the researchers to determine whether we will be able to safely insert the probes into your thigh muscle during the following visit.

Study Visit

1. You will return to Dr. Halliwill's lab for a study visit. This visit will take approximately six hours. You will need to wear a t-shirt and shorts. Prior to arrival you will need to adjust your activities to refrain from:
    a. Eating for at least two hours before arrival.
    b. Consuming caffeine (for example, coffee, tea, red bull, coke, etc.) for at least 10 hours before arrival.
    c. Vitamins, supplements, over-the-counter medications, and prescription drugs (except oral contraceptives) for 24 hours before arrival. If you use oral contraceptives, you should take this when you normally do so.
    d. Consuming alcohol or recreational drugs for 24 hours before arrival.
    e. Moderate or vigorous exercise for 24 hours before arrival.

2. If you are a person of childbearing potential, you will be asked to undergo a pregnancy test during the study visit. For this test, you will be asked to collect a sample of urine in a private restroom. If the test is positive, indicating that you are pregnant, you will not be allowed to participate and will be advised to see your physician or the University of Oregon Health Center.

3. A small needle will be used to obtain blood samples from a vein in your arm or hand, as they would for a routine blood test at the doctor's office. The blood samples will be used to measure factors related to histamine release. The samples will either be analyzed by us or by a commercial lab that will only receive coded samples with no other identifying information.

4. Your heart rate will be monitored by electrocardiogram electrodes placed on the skin near your left and right shoulder and by your left hip. Your blood pressure will be measured at periodic intervals by the inflation of a blood pressure cuff around your arm.

5. You will undergo the following procedure. You will have three small probes (one is called a "thermocouple" and the other two are called "microdialysis fibers") placed into the vastus lateralis (outer thigh muscle). First, the area

of skin where each probe will enter will be numbed with a local anesthetic. Then a small needle will be placed through the skin and into the muscle. The small probe will be passed through the needle, and then the needle will be withdrawn, leaving the small probe in your muscle (about 1-2 inches). This will be done for each of the three probes. The probes will remain in place throughout the rest of the study. There may be some discomfort during the insertion of the small probes into your muscle. We will use a local anesthetic to numb skin where the probes will be inserted to minimize this discomfort, but you may feel pressure or a dull ache in the muscle as the needle moves through the muscle. The thermocouple is used to measure the temperature within the muscle. All the probes will be placed in your muscle for 4-5 hours.

6.The microdialysis probes will be infused with ethanol. This is used to determine how much blood flow the muscle receives. You should not feel anything when this drug is infused into your muscle. One microdialysis probe will be used to infuse small doses of the drug alpha-fluoromethylhistidine, which will prevent your body from producing histamine in the local area around the probe. You should not feel anything when this drug infuses into your muscle.

7. For this particular study, we are using pulsed short-wave diathermy as the way to heat the muscle. In brief, for short-wave pulse diathermy, a heating coil will be placed close to the skin of your thigh; however, it will not contact the surface of your skin. During this time of heating, you may feel an itching sensation as time progresses, but this is a normal response. If you experience any pain or burning, please inform the investigator immediately. The purpose of this heating modality is to increase the temperature of your muscle to around 100ºF. As skin temperatures above 111ºF can feel painful to some, we will keep your skin temperature below 108ºF. For comparison, the temperature of water in hot tubs is routinely 102-104ºF. We will heat your thigh for 100 minutes.

8. At the end of the study visit, the probes will be withdrawn from your leg and a sterile dressing will be applied. You are likely to experience some swelling or redness. Any swelling or redness after the study should be gone a few hours after completion of the study, but you will likely feel some muscle soreness for several days. You will be given some ibuprofen (e.g., Advil or Motrin) to relieve some of the initial soreness. Taking the ibuprofen is not part of the study and is completely optional. You should avoid submerging the site in standing water (e.g., hot tubs, lakes, baths, etc.) and refrain from high-intensity exercise for the two days following the procedure. Although the small probes are sterile, there is a slight risk of infection at the sites where the probes were placed. You will be instructed on how to keep the area clean for a day or two following the study and will need to inform the researchers immediately if you have any redness or swelling in the area.

9. You should notify the investigator immediately if you feel any significant discomfort or concern about your well-being at any time during the study visit.

We will tell you about any new information that may affect your willingness to continue participation in this research.

What happens to the information collected for this research?

Information and specimens collected for this research will be used to determine if heat is a possible stimulus for the release of histamine from mast cells during exercise and may be used in published reports and conference presentations. Your name will not be used in any published reports or conference presentations about this study. Identifiers will be removed from identifiable private information collected in this research, which may be used for future research without additional informed consent. Specimens will not be used for commercial profit.

As part of this study, individuals of child-bearing potential will be asked to take a pregnancy test. We will give you the results of your pregnancy test if it is positive and advise you to follow-up with your physician or University of Oregon health center. You would be responsible for all costs associated with any follow-up testing and medical

care. The results of other research tests will not be made available to you because the research is still in an early phase and the reliability of the results is unknown.

How will my privacy and data confidentiality be protected?

We will take measures to protect your privacy including conducting research in a private setting and using secure data collection platforms. Despite taking steps to protect your privacy, we can never fully guarantee your privacy will be protected.

We will take measures to protect the security of all your personal information including coding all data collected in connection with this study by assigning a subject identification number. The document that links your identity with your subject number will be kept in a locked file cabinet or in a password protected document on a password protected computer within a locked office separated from all data. The coded list of names will be destroyed when study results are published or 24 months after your participation, whichever comes first. All blood samples will be destroyed 5 years after your participation. Any information that can be identified with you will remain confidential and will be disclosed only with your permission. Non-identifiable information may be stored by the researchers indefinitely. Despite these precautions to protect the confidentiality of your information, we can never fully guarantee confidentiality of study information.

Individuals and organizations that conduct or monitor this research may be permitted access to and inspect the research records. This may include access to your private information and study data. These individuals and organizations include:

- The Institutional Review Board (IRB) that reviewed this research
- Government regulatory agencies
- The Food and Drug Administration
- The National Institutes of Health/National Institute of Aging

If data is shared with researchers outside of the University of Oregon physiology lab for the purpose of statistical analysis, all personally identifiable information will be removed. The monitors, auditors, IRB, and regulatory authorities will be granted direct access to your original study data for verification of clinical trial procedures and data, without violating your confidentiality, to the extent permitted by applicable laws and regulations. By signing this consent document, you are authorizing such access.

A description of this study will be available on 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.

This research is covered by a Certificate of Confidentiality from the National Institutes of Health. This means that the researchers cannot release or use information, documents, or samples that may identify you in any action or suit unless you say it is okay. They also cannot provide them as evidence unless you have agreed. This protection includes federal, state, or local civil, criminal, administrative, legislative, or other proceedings. An example would be a court subpoena.

There are some important things that you need to know. The Certificate DOES NOT stop reporting that federal, state or local laws require. Some examples are laws that require reporting of child or elder abuse, some communicable diseases, and threats to harm yourself or others. The Certificate CANNOT BE USED to stop a sponsoring United States federal or state government agency from checking records or evaluating programs. The Certificate DOES NOT stop disclosures required by the federal Food and Drug Administration (FDA). The

Certificate also DOES NOT prevent your information from being used for other research if allowed by federal regulations.

Researchers may release information about you when you say it is okay. For example, you may give them permission to release information to insurers, medical providers or any other persons not connected with the research. The Certificate of Confidentiality does not stop you from willingly releasing information about your involvement in this research. It also does not prevent you from having access to your own information.

What are the risks if I participate in this research?

The risks or discomforts of participating in this research include:

Urine pregnancy test. There is a risk of learning about a surprise pregnancy. Please be assured that the results of this test will remain confidential.

Heating (pulsed short-wave diathermy): Heating the skin of your thigh can become painful and there is a risk of burns or tissue damage to the skin. Discomfort does not generally occur below 111ºF, and damage does not generally occur below 113ºF. We will keep your temperature below these levels, but if you experience any pain or burning, please inform the investigator immediately.

Thermocouple and microdialysis probes: There may be some discomfort during the insertion of the small probes into your muscle. We will use a local anesthetic (prilocaine and lidocaine/epinephrine) to numb skin where the probes will be inserted to minimize this discomfort, but you may feel pressure or a dull ache in the muscle as the needle moves through the muscle. At the end of the study, the probes will be withdrawn, and a sterile dressing will be applied. Any swelling or redness after the study should be gone a few hours after completion of the study, but you may feel some muscle soreness for several days. You will be given some ibuprofen (e.g., Advil or Motrin) to relieve some of the initial soreness. Taking the ibuprofen is not part of the study and is completely optional. Although the small probes are sterile, there is a slight risk of infection at the sites where the probes were placed. You will be instructed on how to keep the area clean for a day or two following the study and will need to inform the researchers immediately if you have any redness or swelling in the area. Though the researchers take great care to handle the fibers delicately and make sure they are not disturbed, there is a slight risk that the microdialysis fibers will break while they are in the muscle and no longer function, but this does not increase risk for you and the fiber will be removed at the end of the study like normal. It is possible for you to have an allergic reaction to the microdialysis fibers and/or the drugs being infused through the fibers, but we are not aware of any cases in which this has happened for the model of probes we use. If you experience any discomfort, tell the researchers right away.

Infusions: We will be infusing very small doses of each drug and only into a very small area of your muscle. You should not have any systemic (whole body) effects of these drugs in the doses given in this study, unless you have an allergic reaction. There is a slight risk that you are allergic to one of the drugs being infused during this study; however, an allergic reaction to the drug could include changes in blood pressure and difficulty breathing. Symptoms of an allergic reaction include rash, itching, swelling, severe dizziness and trouble breathing. One drug (alpha-fluoromethylhistidine) is not currently FDA approved for use in humans and has the potential for unknown risks. Any new information that arises during the study related to the safety of the drug will be disclosed to you.

Blood sampling: In total, 120 ml of blood will be withdrawn, which is about half a cup. The total amount drawn throughout the study is far less than the amount donated in a standard hour-long single day blood donation (473 ml or about 2 cups). There is the possibility of bruising, bleeding, or infection at the site of the blood draw. More serious risks such as fainting or clotting are very rare. The risks associated with blood sampling are no more than would be experienced in a doctor's office. To mitigate risks, an experienced researcher will perform the procedure,

and you will be instructed on how to keep the site clean during the days following the study. Bruising is temporary and does not pose any long-term risks, aside from mild discomfort. Pressure will be applied to the site after the procedure to assure that any bleeding is ceased quickly, and bruising is minimized. A bandage or small gauze pressure wrapping will be applied to keep the site protected. Some people faint or feel nauseous or lightheaded when they have their blood drawn. Participants will be lying down during this time and will be monitored in case there is a problem so we can help. Let us know if you are feeling faint.

Prilocaine and Lidocaine/Epinephrine: The risks associated with prilocaine, and lidocaine/epinephrine are similar in character to those observed with other local anesthetics. Some of the more common adverse reactions include nervousness, dizziness, blurred vision, tremor, drowsiness, tinnitus, numbness, disorientation/confusion, sudden onset of hot or cold sensations, hypotension, nausea and vomiting. These symptoms are associated with lidocaine toxicity, which is not expected at the very low volumes of lidocaine used to numb the skin where the probes will be inserted. If an adverse reaction occurs, we will stop giving you prilocaine and lidocaine/epinephrine. There is a very low probability (less than 1%, or less than 1 person in 100) of an allergic reaction to lidocaine occurring. Symptoms of an allergic reaction may include sudden onset of hives/rash/redness at site of injection, difficulty breathing due to swelling in the throat, upper lip sweating/facial sweating tightness in chest area, increase in heart rate or severely depressed blood pressure. If we observe signs or you report symptoms of anaphylaxis (i.e., red rash with hives, swollen throat, chest tightness, elevated heart rate and/or severely depressed blood pressure), an allergic reaction, the study will be stopped, and we will directly call 911. If you have ever had an allergic reaction to prilocaine, lidocaine, or epinephrine, you will not be allowed to participate. The risk of experiencing a severe allergic reaction is a very low probability, but high severity. Slower than normal heartbeat (bradycardia), irregular heart rhythms (arrhythmia) and seizures are also possible if the lidocaine is injected into the bloodstream. Although we do not plan to introduce lidocaine directly into the blood and will take measures to prevent this from occurring, there is a low likelihood that lidocaine could get into the bloodstream and pose these risks, but the risks could be severe.

Confidentiality: Though we take measures to ensure confidentiality (discussed in the "How will my privacy and data confidentiality be protected?" section above), we can never fully guarantee confidentiality.

Emergency Procedures. In the unlikely event of a medical emergency, you will be transported by ambulance to a local emergency facility. In addition to these risks, taking part in this research may have risks that are unknown or currently unforeseeable.

What are the benefits of participating in this research?

You may or may not benefit from participating in this research. This study will not make your health better. Measurements are not being conducted for diagnostic purposes. The results will not be reviewed by a physician. The purpose of this study is to provide more information on what causes blood flow increases to occur after exercise. Our hope is that by better understanding the physiology of how the human body responds to exercise, we will be better able to use exercise in the prevention and treatment of diseases such as hypertension (high blood pressure) and other forms of cardiovascular disease.

What are my responsibilities if I choose to participate in this research?

If you take part in this research, you will be responsible for:

- Adhering to scheduled sessions and communicating with the researchers in the event that you need to reschedule any sessions.
- Adhering to instructions from the researchers regarding when you need to fast, refrain from consuming caffeine or medications, and abstain from alcohol or exercise.

What other choices do I have besides participation in this research?

It is your choice to participate or not to participate in this research.

What if I want to stop participating in this research?

Taking part in this research study is your decision. Your participation in this study is voluntary. You do not have to take part in this study, but if you do, you can stop at any time. You have the right to choose not to participate in any study activity or completely withdraw from continued participation at any point in this study without penalty or loss of benefits to which you are otherwise entitled. The data collected on you to the point of withdrawal remains part of the study database and may not be removed. Your decision whether or not to participate will not affect your relationship with the researchers or the University of Oregon.

Will it cost me money to take part in this research?

You will not pay for any tests or procedures that are done just for this research study.

What if I am injured because of participating in this research?

If you are injured or get sick because of being in this research, call the researchers immediately.

In the event you suffer a research-related injury your medical expenses will be your responsibility or that of your insurance company (or other third-party payer), although you are not precluded from seeking to collect compensation for injury related to malpractice, fault, or blame on the part of those involved in the research. If you are a UO student or employee and are covered by a UO medical plan, that plan might have terms that apply to your injury.

If you experience harm because of the project, you can ask the State of Oregon to pay you. If you have been harmed, there are two University representatives you need to contact. Here are their addresses and phone numbers:

General Counsel/ Office of the President
1226 University of Oregon
Eugene, OR 97403-1226
(541) 346-3082

Research Compliance Services
5237 University of Oregon
Eugene, OR 97403-5237
(541) 346-2510

A law called the Oregon Tort Claims Act may limit the amount of money you can receive from the State of Oregon if you are harmed.

Will I be paid for participating in this research?

You will get $105 for participating in this study. This money is for the inconvenience and time you spent in this study. If you start the study but stop before the study has ended, the amount of money you receive will be pro-rated at a rate of $15 per hour that you complete. There is no compensation for completing only the screening process.

Please be aware, compensation for participation in research may be considered taxable income. The University requires tracking for compensation that is paid to you; this may include your name and contact information. This information is stored confidentially and separate from research data. If you receive $600 or more in a calendar year, you may be contacted to provide additional information (e.g., Social Security Number) for tax reporting purposes.

Who can answer my questions about this research?

If you have questions, concerns, or have experienced a research related injury, contact the research team at:

Dr. John Halliwill
541-346-7591
halliwil@uoregon.edu

An Institutional Review Board ("IRB") is overseeing this research. An IRB is a group of people who perform independent review of research studies to ensure the rights and welfare of participants are protected. UO Research Compliance Services is the office that supports the IRB. If you have questions about your rights or wish to speak with someone other than the research team, you may contact:

Research Compliance Services
5237 University of Oregon
Eugene, OR 97403-5237
(541) 346-2510

STATEMENT OF CONSENT

I have had the opportunity to read and consider the information in this form. I have asked any questions necessary to make a decision about my participation. I understand that I can ask additional questions throughout my participation.

I understand that by signing below, I volunteer to participate in this research. I understand that I am not waiving any legal rights. I have been provided with a copy of this consent form. I understand that if my ability to consent or assent for myself changes, either I or my legal representative may be asked to re-consent prior to my continued participation in this study.

I consent to participate in this study.

Name of Adult Participant	Signature of Adult Participant	Date

Researcher Signature (to be completed at time of informed consent)

I have explained the research to the participant and answered all of his/her questions. I believe that he/she understands the information described in this consent form and freely consents to participate.

Name of Research Team Member	Signature of Research Team Member	Date

UNIVERSITY OF OREGON

Consent for Research Participation

Title:	Histamine as a Molecular Transducer of Adaptation to Exercise (Aim 1b)
Sponsor:	NIH
Researcher(s):	John R Halliwill, Ph.D. and colleagues, University of Oregon
Researcher Contact Info:	541-346-7591
	halliwil@uoregon.edu

You are being asked to participate in a research study. The box below highlights key information about this research for you to consider when making a decision whether or not to participate. Carefully consider this information and the more detailed information provided below the box. Please ask questions about any of the information you do not understand before you decide whether to participate.

Key Information for You to Consider

- **Voluntary Consent**. You are being asked to volunteer for a research study. It is up to you whether you choose to participate or not. There will be no penalty or loss of benefits to which you are otherwise entitled if you choose not to participate or discontinue participation.
- **Purpose**. The purpose of this research is to determine what signal released by skeletal muscle induces the release of histamine in response to exercise.
- **Duration.** It is expected that your participation will last 8 hours over 3 days.
- **Procedures and Activities.** You will be asked to participate in a maximal exercise test, 60 minutes of one-legged knee extensions, and several clinical tests including a blood draw and infusion of saline through microdialysis.
- **Risks.** Some of the foreseeable risks or discomforts of your participation include those associated with maximal exercise such as muscle soreness, allergic reaction to local anesthetic, infection at site of blood collection or microdialysis probe placement, nausea, vomiting and light-headedness, and the rare possibility of heart related events.
- **Benefits**. No direct benefit but the researchers hope to learn what causes blood flow increases to occur after exercise.
- **Alternatives.** Participation is voluntary and the only alternative is to not participate.

Why is this research being done?

Exercise promotes and maintains healthy cardiovascular, musculoskeletal, and metabolic function, but the signals and mechanisms which bring about these effects are poorly understood. The long-term goal of this proposal is to determine the factors that regulate exercise's effects on the health of blood vessels and skeletal muscle. Previous studies have shown that exercise induces the release of histamine within skeletal muscle.

The purpose of the research is to determine what signal released by skeletal muscle makes this happen This protocol will use fluid collected from your skeletal muscle before, during, and after exercise to determine the effect of histamine on blood vessel properties. This topic is both clinically and scientifically important. As such, this study is currently funded by the National Institutes of Health. You are being asked to participate because you are a young healthy individual, who is either sedentary, recreationally active, or a trained athlete and free from any known cardiovascular disease. About 42 people will take part in this research.

How long will I be in this research?

We expect that your participation will last 8 hours over 3 days (one screening visit, one exercise test visit, and one study visit). The first visit will last one hour. The exercise test visit will also last one hour. The study visit will last six hours.

What happens if I agree to participate in this research?

If you agree to be in this research, your participation will include a screening visit, an exercise test visit, and a study visit.

Screening Visit

You will arrive at Dr. Halliwill's laboratory at the Bowerman Sports Science Center at Hayward Field at the University of Oregon for a screening visit. This screening visit will take approximately one hour. You will meet with one of the investigators of the study to discuss the project, to see the laboratory, and to read this form. To determine if you fit the inclusion criteria for the study, you will be asked questions about your health history, you will be given a physical activity questionnaire which will allow investigators to determine your activity level, and your height, weight, and resting blood pressure will be measured. You may also undergo Doppler ultrasonography of your thigh (vastus lateralis muscle). A small probe (ultrasound Doppler probe) will be held on your thigh to image the muscle. The probe uses ultrasound waves to identify tissues in the leg.

Exercise Test Visit

1. You will return to Dr. Halliwill's lab for an exercise test visit. This visit will take approximately one hour. You will need to wear a t-shirt and shorts. Prior to arrival you will need to adjust your activities to refrain from:
    a. Eating for at least two hours before arrival.
    b. Consuming caffeine (for example, coffee, tea, red bull, coke, etc.) for at least 10 hours before arrival.
    c. Vitamins, supplements, over-the-counter medications, and prescription drugs (except oral contraceptives) for 24 hours before arrival. If you use oral contraceptives, you should take this when you normally do so.
    d. Consuming alcohol or recreational drugs for 24 hours before arrival.
    e. Moderate or vigorous exercise for 24 hours before arrival.

2. During the exercise test visit, your heart rate will be monitored by electrocardiogram electrodes placed on the skin near your left and right shoulder and by your left hip. The electrical activity of the muscle in your legs will also be monitored by electromyogram electrodes placed on the skin of the back of your leg and the skin on top of your thigh. Your blood pressure will be measured at periodic intervals by the inflation of a blood pressure cuff around your arm.

3. You will perform one-legged knee extension exercise while seated on an exercise machine that measures how hard you are working. This exercise is like kicking a soccer ball over and over again. After a 5-minute warm-up, you will be asked to maintain a selected kicking rate as the machine increases how hard you work every minute until you reach your peak exercise capacity. It normally takes 10 to 15 minutes for people to reach their peak effort. There is no win/lose threshold or specific value that participants need to achieve; participants simply need to do their best. The total time for either test (including placement of electrodes on your skin, warm-up, exercise, and cool-down) is approximately thirty minutes.

4. You should notify the investigator immediately if you feel any significant discomfort or concern about your well-being at any time during the exercise test visit. Some examples of discomfort include fatigue and muscle soreness.

This session will serve to familiarize you with the procedures to be used on the study day. It will also establish your peak exercise capacity on the exercise machine and therefore will be used to establish the appropriate workload for the exercise session on the study day.

Study Visit

1. You will return to Dr. Halliwill's lab for a study visit. This visit will take approximately six hours. You will need to wear a t-shirt and shorts. Prior to arrival you will need to adjust your activities to refrain from:
    a. Eating for at least two hours before arrival.
    b. Consuming caffeine (for example, coffee, tea, red bull, coke, etc.) for at least 10 hours before arrival.
    c. Nutritional supplements, vitamins, over-the-counter medications, and prescription drugs (except oral contraceptives) for 24 hours before arrival. If you use oral contraceptives, you should take this when you normally do so.
    d. Consuming alcohol or recreational drugs for 24 hours before arrival.
    e. Moderate or vigorous exercise for 24 hours before arrival.

2. If you are a person of childbearing potential, you will be asked to undergo a pregnancy test during the study visit. For this test, you will be asked to collect a sample of urine in a private restroom. If the test is positive, indicating that you are pregnant, you will not be allowed to participate and will be advised to see your physician or the University of Oregon Health Center.

3. A small needle will be used to obtain blood samples from a vein in your arm or hand, as they would for a routine blood test at the doctor's office. The blood samples will be used to measure factors related to histamine release. The samples will either be analyzed by us or by a commercial lab that will only receive coded samples with no other identifying information.

4. Your heart rate will be monitored by electrocardiogram electrodes placed on the skin near your left and right shoulder and by your left hip. The electrical activity of the muscle in your legs will also be monitored by electromyogram electrodes placed on the skin of the back of your leg and the skin on top of your thigh. Your blood pressure will be measured at periodic intervals by the inflation of a blood pressure cuff around your arm.

5. During the study visit, you will perform one-legged knee extension exercise while seated on an exercise machine that measures how hard you are working. During this exercise session you will be asked to maintain a selected kicking rate for 60 minutes.

6. Before and after the exercise session, a small probe (ultrasound Doppler probe) will be held on an area of skin at your groin-hip intersection to image your femoral artery. The probe uses ultrasound waves to measure blood flow in these arteries. The femoral artery will be studied for 10 minutes before you exercise and for one hour after you exercise.

7. You will undergo the following procedure. You will have two small probes (called "microdialysis fibers") placed into the vastus lateralis (outer thigh muscle). First, the area of skin where each probe will enter will be numbed with a local anesthetic (prilocaine and lidocaine/epinephrine). Then a small needle will be placed through the skin and into the muscle. The small probe will be passed through the needle, and then the needle will be withdrawn, leaving the small probe in your muscle (about 1-2 inches). This will be done for each of the two probes. The probes will remain in place throughout the rest of the study. There may be some discomfort during the insertion of the small probes into your muscle. We will use a local anesthetic to numb skin where the probes will be inserted to minimize this discomfort, but you may feel pressure or a dull ache in the muscle as the needle moves through the muscle. All the probes will be placed in your muscle for 4-5 hours.

8. The microdialysis probes will be used to infuse saline. This will allow us to collect a sample of the fluid surrounding the muscle before, during, and after you exercise. You should not feel anything when saline infuses into your muscle.

9. At the end of the study visit, the probes will be withdrawn from your leg and a sterile dressing will be applied. You are likely to experience some swelling or redness. Any swelling or redness after the study should be gone a few hours after completion of the study, but you will likely feel some muscle soreness for several days. You will be given some ibuprofen (e.g., Advil or Motrin) to relieve some of the initial soreness. Taking the ibuprofen is not part of the study and is completely optional. You should avoid submerging the site in standing water (e.g., hot tubs, lakes, baths, etc.) and refrain from high-intensity exercise for the two days following the procedure. Although the small probes are sterile, there is a slight risk of infection at the sites where the probes were placed. You will be instructed on how to keep the area clean for a day or two following the study and will need to inform the researchers immediately if you have any redness or swelling in the area.

10. You should notify the investigator immediately if you feel any significant discomfort or concern about your well-being at any time during the study visit.

We will tell you about any new information that may affect your willingness to continue participation in this research.

What happens to the information collected for this research?

Information and specimens collected for this research will be used to determine what signal released by skeletal muscle during exercise leads to release of histamine within the muscle and may be used in published reports and conference presentations. Your name will not be used in any published reports or conference presentations about this study. Identifiers will be removed from identifiable private information collected in this research, which may be used for future research without additional informed consent. Specimens will not be used for commercial profit.

As part of this study, individuals of child-bearing potential will be asked to take a pregnancy test. We will give you the results of your pregnancy test if it is positive and advise you to follow-up with your physician or University of Oregon health center. You would be responsible for all costs associated with any follow-up testing and medical care. The results of other research tests will not be made available to you because the research is still in an early phase and the reliability of the results is unknown.

How will my privacy and data confidentiality be protected?

We will take measures to protect your privacy including conducting research in a private setting and using secure data collection platforms. Despite taking steps to protect your privacy, we can never fully guarantee your privacy will be protected.

We will take measures to protect the security of all your personal information including coding all data collected in connection with this study by assigning a subject identification number. The document that links your identity with your subject number will be kept in a locked file cabinet within or in a password protected document on a password protective computer within a locked office separated from all data. The coded list of names will be destroyed when study results are published or 24 months after your participation, whichever comes first. All blood samples will be destroyed 5 years after your participation. Any information that can be identified with you will remain confidential and will be disclosed only with your permission. Non-identifiable information may be stored by the researchers indefinitely. Despite these precautions to protect the confidentiality of your information, we can never fully guarantee confidentiality of study information.

Individuals and organizations that conduct or monitor this research may be permitted access to and inspect the research records. This may include access to your private information and study data. These individuals and organizations include:

- The Institutional Review Board (IRB) that reviewed this research
- Government regulatory agencies
- The Food and Drug Administration
- The National Institutes of Health/National Institute of Aging

If data is shared with researchers outside of the University of Oregon physiology lab for the purpose of statistical analysis, all personally identifiable information will be removed. The monitors, auditors, IRB, and regulatory authorities will be granted direct access to your original study data for verification of clinical trial procedures and data, without violating your confidentiality, to the extent permitted by applicable laws and regulations. By signing this consent document, you are authorizing such access.

A description of this study will be available on 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.

This research is covered by a Certificate of Confidentiality from the National Institutes of Health. This means that the researchers cannot release or use information, documents, or samples that may identify you in any action or suit unless you say it is okay. They also cannot provide them as evidence unless you have agreed. This protection includes federal, state, or local civil, criminal, administrative, legislative, or other proceedings. An example would be a court subpoena.

There are some important things that you need to know. The Certificate DOES NOT stop reporting that federal, state or local laws require. Some examples are laws that require reporting of child or elder abuse, some communicable diseases, and threats to harm yourself or others. The Certificate CANNOT BE USED to stop a sponsoring United States federal or state government agency from checking records or evaluating programs. The Certificate DOES NOT stop disclosures required by the federal Food and Drug Administration (FDA). The Certificate also DOES NOT prevent your information from being used for other research if allowed by federal regulations.

Researchers may release information about you when you say it is okay. For example, you may give them permission to release information to insurers, medical providers or any other persons not connected with the research. The Certificate of Confidentiality does not stop you from willingly releasing information about your involvement in this research. It also does not prevent you from having access to your own information.

What are the risks if I participate in this research?

The risks or discomforts of participating in this research include:

Urine pregnancy test: There is a risk of learning about a surprise pregnancy. Please be assured that the results of this test will remain confidential.

Microdialysis probes: There may be some discomfort during the insertion of the small probes into your muscle. We will use a local anesthetic (prilocaine and lidocaine/epinephrine) to numb skin where the probes will be inserted to minimize this discomfort, but you may feel pressure or a dull ache in the muscle as the needle moves through the muscle. At the end of the study, the probe will be withdrawn and a sterile dressing will be applied.

Any swelling or redness after the study should be gone a few hours after completion of the study, but you may feel some muscle soreness for several days. You will be given some ibuprofen (e.g., Advil or Motrin) to relieve some of the initial soreness. Taking the ibuprofen is not part of the study and is completely optional. Although the small probes are sterile, there is a slight risk of infection at the sites where the probes were placed. You will be instructed on how to keep the area clean for a day or two following the study and will need to inform the researchers immediately if you have any redness or swelling in the area. Though the researchers take greater care to handle fibers delicately and make sure they are not disturbed, there is a slight risk that the microdialysis fibers will break while they are in the muscle and no longer function, but this does not increase risk for you and the fiber will be removed at the end of the study like normal. It is possible for you to have an allergic reaction to the microdialysis fibers and/or the fluid being infused through the fibers, but we are not aware of any cases in which this has happened for the model of probes we use. If you experience any discomfort, tell the researchers right away.

Infusions: We will be infusing saline into a very small area of your muscle or skin. You should not have any systemic (whole body) effects to infusion of saline.

Blood sampling: In total, 120 ml of blood will be withdrawn, which is about half a cup. The total amount drawn throughout the study is far less than the amount donated in a standard hour-long single day blood donation (473 ml or about 2 cups). There is the possibility of bruising, bleeding, or infection at the site of the blood draw. More serious risks such as fainting or clotting are very rare. The risks associated with blood sampling are no more than would be experienced in a doctor's office. To mitigate risks, an experienced researcher will perform the procedure and you will be instructed on how to keep the site clean during the days following the study. Bruising is temporary and does not pose any long-term risks, aside from mild discomfort. Pressure will be applied to the site after the procedure to assure that any bleeding is ceased quickly, and bruising is minimized. A bandage or small gauze pressure wrapping will be applied to keep the site protected. Some people faint or feel nauseous or lightheaded when they have their blood drawn. Participants will be lying down during this time and will be monitored in case there is a problem so we can help. Let us know if you are feeling faint.

Exercise test: This test involves exercise with just one leg until it becomes fatigued. The risks associated with exercise include light-headedness, fatigue, shortness of breath, nausea, vomiting, risk of heart attack and death. The risk of death during or immediately after an exercise test is <0.01% (less than 1 out of 10,000). The risk of heart attack during or immediately after an exercise test is <0.04% (less than 2 out of 5,000). The risk of complication requiring hospitalization is approximately 0.1% (1 out of 1000). Heart activity and blood pressure will be monitored during testing to ensure your safety. We will stop the testing immediately if you feel light-headed, nauseated, or experience any other unpleasant symptoms. The risk of complications is very low in young healthy subjects.

Prilocaine and Lidocaine/Epinephrine: The risks associated with prilocaine, and lidocaine/epinephrine are similar in character to those observed with other local anesthetics. Some of the more common adverse reactions include nervousness, dizziness, blurred vision, tremor, drowsiness, tinnitus, numbness, disorientation/confusion, sudden onset of hot or cold sensations, hypotension, nausea and vomiting. These symptoms are associated with lidocaine toxicity, which is not expected at the very low volumes of lidocaine used to numb the skin where the probes will be inserted. If an adverse reaction occurs, we will stop giving you prilocaine and lidocaine/epinephrine. There is a very low probability (less than 1%, or less than 1 person in 100) of an allergic reaction to lidocaine occurring. Symptoms of an allergic reaction may include sudden onset of hives/rash/redness at site of injection, difficulty breathing due to swelling in the throat, upper lip sweating/facial sweating tightness in chest area, increase in heart rate or severely depressed blood pressure. If we observe signs or you report symptoms of anaphylaxis (i.e., red rash with hives, swollen throat, chest tightness, elevated heart rate and/or severely depressed blood pressure), an allergic reaction, the study will be stopped, and we will directly call 911. If you have ever had an allergic reaction to

prilocaine, lidocaine, or epinephrine, you will not be allowed to participate. The risk of experiencing a severe allergic reaction is a very low probability, but high severity. Slower than normal heartbeat (bradycardia), irregular heart rhythms (arrhythmia) and seizures are also possible if the lidocaine is injected into the bloodstream. Although we do not plan to introduce lidocaine directly into the blood and will take measures to prevent this from occurring, there is a low likelihood that lidocaine could get into the bloodstream and pose these risks, but the risks could be severe.

Confidentiality: Though we take measures to ensure confidentiality (discussed in the "How will my privacy and data confidentiality be protected?" section above), we can never fully guarantee confidentiality.

Emergency Procedures. In the unlikely event of a medical emergency, you will be transported by ambulance to a local emergency facility. In addition to these risks, taking part in this research may have risks that are unknown or currently unforeseeable.

What are the benefits of participating in this research?

You may or may not benefit from participating in this research. This study will not make your health better. Measurements are not being conducted for diagnostic purposes. The results will not be reviewed by a physician. The purpose of this study is to provide more information on what causes blood flow increases to occur after exercise. Our hope is that by better understanding the physiology of how the human body responds to exercise, we will be better able to use exercise in the prevention and treatment of diseases such as hypertension (high blood pressure) and other forms of cardiovascular disease.

What are my responsibilities if I choose to participate in this research?

If you take part in this research, you will be responsible for:

- Adhering to scheduled sessions and communicating with the researchers in the event that you need to reschedule any sessions.
- Adhering to instructions from the researchers regarding when you need to fast, refrain from consuming caffeine or medications, and abstain from alcohol or exercise.

What other choices do I have besides participation in this research?

It is your choice to participate or not to participate in this research.

What if I want to stop participating in this research?

Taking part in this research study is your decision. Your participation in this study is voluntary. You do not have to take part in this study, but if you do, you can stop at any time. You have the right to choose not to participate in any study activity or completely withdraw from continued participation at any point in this study without penalty or loss of benefits to which you are otherwise entitled. The data collected on you to the point of withdrawal remains part of the study database and may not be removed. Your decision whether or not to participate will not affect your relationship with the researchers or the University of Oregon.

Will it cost me money to take part in this research?

You will not pay for any tests or procedures that are done just for this research study.

What if I am injured because of participating in this research?

If you are injured or get sick because of being in this research, call the researchers immediately.

In the event you suffer a research-related injury your medical expenses will be your responsibility or that of your insurance company (or other third-party payer), although you are not precluded from seeking to collect compensation for injury related to malpractice, fault, or blame on the part of those involved in the research. If you are a UO student or employee and are covered by a UO medical plan, that plan might have terms that apply to your injury.

If you experience harm because of the project, you can ask the State of Oregon to pay you. If you have been harmed, there are two University representatives you need to contact. Here are their addresses and phone numbers:

General Counsel/ Office of the President
1226 University of Oregon
Eugene, OR 97403-1226
(541) 346-3082

Research Compliance Services
5237 University of Oregon
Eugene, OR 97403-5237
(541) 346-2510

A law called the Oregon Tort Claims Act may limit the amount of money you can receive from the State of Oregon if you are harmed.

Will I be paid for participating in this research?

You will get $120 for participating in this study. This money is for the inconvenience and time you spent in this study. If you start the study but stop before the study has ended, the amount of money you receive will be pro-rated at a rate of $15 per hour that you complete. There is no compensation for completing only the screening process.

Please be aware, compensation for participation in research may be considered taxable income. The University requires tracking for compensation that is paid to you; this may include your name and contact information. This information is stored confidentially and separate from research data. If you receive $600 or more in a calendar year, you may be contacted to provide additional information (e.g., Social Security Number) for tax reporting purposes.

Who can answer my questions about this research?

If you have questions, concerns, or have experienced a research related injury, contact the research team at:

Dr. John Halliwill
541-346-7591
halliwil@uoregon.edu

An Institutional Review Board ("IRB") is overseeing this research. An IRB is a group of people who perform independent review of research studies to ensure the rights and welfare of participants are protected. UO Research Compliance Services is the office that supports the IRB. If you have questions about your rights or wish to speak with someone other than the research team, you may contact:

UNIVERSITY OF OREGON

Research Compliance Services
5237 University of Oregon
Eugene, OR 97403-5237
(541) 346-2510

STATEMENT OF CONSENT

I have had the opportunity to read and consider the information in this form. I have asked any questions necessary to make a decision about my participation. I understand that I can ask additional questions throughout my participation.

I understand that by signing below, I volunteer to participate in this research. I understand that I am not waiving any legal rights. I have been provided with a copy of this consent form. I understand that if my ability to consent or assent for myself changes, either I or my legal representative may be asked to re-consent prior to my continued participation in this study.

I consent to participate in this study.

Name of Adult Participant	Signature of Adult Participant	Date

Researcher Signature (to be completed at time of informed consent)

I have explained the research to the participant and answered all of his/her questions. I believe that he/she understands the information described in this consent form and freely consents to participate.

Name of Research Team Member	Signature of Research Team Member	Date