

Sex Differences in the Dilatory Response of Compound 21

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INFORMED CONSENT DOCUMENT

Project Title: **Sex Differences in the Dilatory Response of Compound 21**

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This consent form describes the research study to help you decide if you want to participate. This form provides important information about what you will be asked to do during the study, about the risks and benefits of the study, and about your rights as a research subject.

- If you have any questions about or do not understand something in this form, you should ask the research team for more information.
- You should discuss your participation with anyone you choose such as family or friends.
- Do not agree to participate in this study unless the research team has answered your questions and you decide that you want to be part of this study.

WHAT IS THE PURPOSE OF THIS STUDY?

This is a research study. We are inviting you to participate in this research study because you are between the ages of 18-35 years old and have a body mass index (BMI) between 18 and 30 kg/m².

When your blood pressure decreases, your body responds by naturally producing and releasing a chemical called Angiotensin II into your bloodstream. This substance acts through Angiotensin II type I receptors (AT₁R) on blood vessels causing them to become smaller in diameter (i.e., vasoconstriction). Angiotensin II also acts through lesser-known Angiotensin II type II receptors (AT₂R) to cause your blood vessels to increase in diameter (i.e., vasodilation). Normally, these two receptors work in balance to maintain your blood pressure. Excess release of Angiotensin II may reduce the sensitivity of AT₂Rs and increase AT₁R activation, which plays a major role in cardiovascular diseases. Previous work has shown that Angiotensin II is reduced by estrogen in pre-menopausal women, leading to an enhanced effect of AT₂Rs that is not seen in age-matched men. The purpose of this study is to examine the sex difference in young adults to Compound 21 (C21), which activates AT₂Rs. We anticipate the outcomes of this study will aid in the understanding of mechanisms of Angiotensin II receptors in men and women and how AT₂R activation with C21 may restore their balance.

This study includes the use of four research drugs in a nickel-sized area of skin on your arm. They are losartan, C21, Lactated Ringer's solution, and sodium nitroprusside. These drugs are considered investigational, which means that they have not been approved by the U.S. Food and Drug Administration for this use.

HOW MANY PEOPLE WILL PARTICIPATE?

Approximately 44 people will take part in this study conducted by investigators at the University of Iowa.

HOW LONG WILL I BE IN THIS STUDY?

If you agree to take part in this study, your involvement will last for approximately 2 weeks depending on your availability.

- **Screening Visit** **up to 1 hour**
- **Study Visit** **up to 4 hours**

In the event of an experimental failure (e.g. equipment stops working, power outage in the building during study visit, etc.) you may be asked to repeat a trial. The decision to repeat a trial is up to you. If you do repeat a trial, you will be compensated for that additional trial.

WHAT WILL HAPPEN DURING THIS STUDY?

Screening Visit:

The researchers will measure your height, weight, blood pressure, and heart rate.

- You will fill out a participant information survey and health history questionnaire. You can skip any questions that you do not want to answer.
- Women will submit a urine sample for a pregnancy test.

We will use the information collected during the screening visit to determine if you are eligible to continue in the study, and to analyze our data in the study.

Study Visit (Microdialysis Experiment):

Before you arrive:

If you have any questions about the study, please contact us right away. You will be asked to fast 3 hours prior to your appointment, avoid caffeine 12 hours prior, avoid alcohol and any forms of heavy exercise 24 hours prior, and avoid supplements and over-the-counter medications on the morning of the experiment visit. Do not stop taking medications as prescribed by your physician.

Women who complete the study will be tested during the early follicular phase of the menstrual cycle (1-7 days after the onset of menses) or during the placebo phase of an oral contraceptive. You will schedule with the research team to make sure you are scheduled during the right time.

When you arrive:

The researchers will meet you at the entrance of the Field House and walk with you to the lab space (528 FH) for the blood draw and experiment. The blood draw involves approved laboratory personnel drawing 15 ml (~1 Tbsp) of blood from a vein in your arm. We save some of the blood in the research lab to analyze later.

Measurements:

Blood Pressure, Heart Rate: We measure blood pressure and heart rate throughout the experiment. We apply three sticky tabs to the skin of your chest. The tabs connect to an electrocardiogram (ECG) machine that records heart rate. During the experiment, we can measure blood pressure in one of two ways.

A) We inflate a cuff on your upper arm while we listen at the inside of your elbow with a

stethoscope, or

B) An automated machine inflates a cuff on the upper arm and uses a sensor in the cuff to measure blood pressure.

Skin Blood Flow, Skin Temperature: We measure skin blood flow and skin temperature throughout the experiment. We tape a thin probe and its holder over two sites on your forearm. The thin probe measures skin blood flow with a weak laser light (Laser Doppler Flowmetry). The holders measure skin temperature. We control the temperature of the holders. The holders start at 33°C (91°F).

Microdialysis (MD):

Overview: Microdialysis (MD) involves placing very thin plastic tubing between the layers of your skin. The largest part of the tubing is about 6 times the diameter of a human hair. We pump fluid like that found in your body's tissues (lactated Ringer's solution) through the thin tubing. The thin tubing acts like the very small blood vessels in your skin. There is an exchange of substances between the fluid in the tubing and the fluid in the surrounding tissue. During the experiment, we add substances to the fluid in the tubing. The substances can only reach a 2.5 cm² (0.4 inch²), nickel-sized area of skin.

MD Probe Insertion: We place a tight band around your arm so we can easily see your veins. For each MD site, we make pairs of pen-marks 2.5 cm (1 inch) apart and away from veins. The MD tubing enters and exits your skin at the marks. We remove the tight band. We clean your arm with an orange-colored fluid and alcohol. We place an ice bag on your arm for 5 minutes to numb your skin. Then we insert a thin needle into your skin at each entry mark. The needle's tip travels between the layers of skin for 2.5 cm (1 inch). It leaves your skin at the matching exit mark. We thread the MD tubing through the needle. Next, we withdraw the needle leaving the tubing in your skin. We prepare all MD sites in this manner. Any redness of your skin subsides in about 60 – 120 minutes.

Microdialysis Experiment Protocol:

Summary: We prepare 2 MD sites as described above. Initially, Lactated Ringer's only flows through all probes. Then the investigational agents are added to the Lactated Ringer's flowing through MD probe 2 for 60 minutes. After those 60 minutes, we record baseline measurements for both sites (20 minutes). After we have collected baseline data, we change the fluid flowing through each microdialysis fiber at 10-minute intervals. Each perfusion will include a progressively higher concentration of C21. After the last amounts of C21 have been added, all MD sites are then warmed to 43°C (108°F) to perform Maximal Skin Blood Flow. At the same time, the researchers switch the fluids at all sites to Ringer's + Sodium Nitroprusside (SNP) for about 30 minutes. This causes blood vessels at the MD sites to dilate or enlarge as much as they can. Finally, we remove the MD probes and apply a sterile dressing. If desired, we can place a bag of ice on your arm for 10 minutes to reduce any bruising that may occur. We remove all instrumentation and measure your blood pressure and heart rate before you leave.

The 2 MD sites are:

C21 Dose Response:

Probe 1. Lactated Ringer's only

Probe 2. Lactated Ringer's + Losartan

Tissue/Blood/Data Storage for Future Use

As part of this study, we are obtaining blood samples from you. We would like to study your blood in the future after this study is over. Your sample, information, and/or data may be placed in a central repository or other national repositories sponsored by the National Institutes of Health or other Federal agencies. If this happens, it will be stripped of identifiers (such as name, date of birth, address, etc). Other qualified researchers who obtain proper permission may gain access to your sample and/or data for use in approved research studies that may or may not be related to in the purpose of this study.

The tests we might want to use to study your blood may not even exist at this time. Therefore, we are asking for your permission to store your blood so that we can study them in the future. These future studies may provide additional information that will be helpful in understanding cardiovascular disease, but it is unlikely that what we learn from these studies will have a direct benefit to you. It is possible that your blood might be used to develop products tests, or discoveries that could be patented and licensed. In some instances, these may have potential commercial value and may be developed by the Investigators, University of Iowa, commercial companies, organizations funding this research, or others that may not be working directly with this research team. However, donors of **blood** do not retain any property rights to the materials. Therefore, there are no plans to provide financial compensation to you should this occur.

Your blood will be stored *with a code which may be linked to* your name and date of birth. If you agree now to future use of your blood but decide in the future that you would like to have it removed from future research, you should contact Anna Stanhewicz (319-467-1732, anna-stanhewicz@uiowa.edu). However, if some research with your blood has already been completed, the information from that research may still be used.

Please place your initials in the blank next to Yes or No for each of the questions below:

My blood may be stored/shared for future research in cardiovascular disease.

_____ Yes _____ No

My blood may be stored/shared for future research for any other purpose.

_____ Yes _____ No

WILL I BE NOTIFIED IF MY STUDY VISIT RESULT(S) IN AN UNEXPECTED FINDING?

The results from the skin blood flow data we collect in this research study are not the same quality as what you would receive as part of your routine health care. The results will not be reviewed by a physician who normally reads such results. Due to this, you will not be informed of any unexpected findings. The results of your study will not be placed in your medical record with your primary care physician or otherwise. If you believe you are having symptoms that may require care, you should contact your primary care physician.

WILL YOU KEEP MY NAME ON FILE FOR PARTICIPATION IN FUTURE STUDIES?

If you consent, we may contact you to participate in future studies with our laboratory group. We will keep your name, sex, race/ethnicity, birthdate, and contact information for this purpose. Participating in

this study does not mean that you are obligated to participate in any future studies. A separate consent document would be signed for future studies.

May we keep your name, race/ethnicity, birthdate, pregnancy history, and contact info to contact you for future studies?

Please place your initials in the blank next to Yes or No for each of the questions below:

_____ Yes _____ No

WHAT ARE THE RISKS OF THIS STUDY?

You may experience one or more of the risks indicated below from being in this study. In addition to these, there may be other unknown risks, or risks that we did not anticipate, associated with being in this study.

Microdialysis: The risks are less than that for a blood draw because microdialysis uses only a small, local area of skin. In contrast, a blood draw involves not only skin, but also large blood vessels and blood. You are likely to have some pain and bruising like that from a blood draw. However, we use ice to numb your arm when we insert the tubing. Also, the small needle reduces pain when we insert the tubing. You are not likely to have pain after the tubing is in place. You may feel a little pain when we remove the tubing from your skin. Needles make some people feel lightheaded or cause them to faint. You may feel lightheaded or faint during the placement or the removal of the fibers. Although rare, the tubing could break as we remove it from the skin. Then we remove the tubing still in your skin by pulling on the other end of it. This presents no added risk for you. Even more rare, the tubing could break so that a piece of the tubing is left under your skin. In this case, we treat any tubing still in your skin like a splinter. We stop any mild bleeding with mild pressure and sterile gauze. Infection is possible. We keep the risk of infection very small by using sterile techniques and supplies like those used with blood draws. We apply a sterile bandage to the site after the experiment. We tell you how to take care of the site.

Fluid flowing through the tubing: The substances flowing through the tubing only go to a 2.5 cm² (0.4 inch²) area of skin at each tubing site. The amount that enters the skin is very small. However, there is a chance of having a bad reaction to the substances. This reaction could produce redness, itching, rash, and/or swelling. A worse reaction could also cause fever, breathing problems, changes in pulse, convulsions, and/or fainting. We and other researchers have used these substances with microdialysis in skin. There have been no reports that these substances caused bad reactions. If a bad reaction should occur, we summon medical help.

Losartan, C21, SNP: These substances stop or mimic the action of your body's natural chemicals upon the blood vessels in the skin. A small amount of these substances enters the skin around the tubing. This only affects the blood flow in the vessels in that nickel-sized area of skin. The effect of these substances in your skin is gone within an hour after the experiment. There are no individual risks associated with the substances used with microdialysis. There is a slight chance of allergic reaction to these substances, which could produce redness, itching, rash, and/or swelling.

Losartan – causes blood vessels to constrict (get narrow).

Compound 21 (C21) – causes blood vessels to dilate (get wider).

Sodium Nitroprusside (SNP) – causes blood vessels to dilate as much as they can.

Lactated Ringer’s Solution: This fluid is similar to the natural fluids in your skin. This fluid contains salt, potassium, lactate, and chloride. The acid content is like that in your body’s natural fluids. A bad reaction to this fluid is highly unlikely, but could produce redness, itching, rash, and/or swelling..

Laser Doppler Flowmetry: Weak lasers can hurt your eye if you stare into the light for a long time. We do not turn on the laser until the probes are taped to a surface. The tape may irritate your skin.

Blood Pressure: The researchers measure blood pressure with the method used in a doctor’s office and they can use a machine. A cuff inflates on the upper arm. As the cuff slowly deflates, the researchers listen with a stethoscope at the bend in the elbow or the machine takes a reading. During the short time the researchers inflate the cuff, your arm may feel numb or tingly. The cuff could cause mild bruising.

Povidone Iodine: Researchers and hospitals use this orange-colored fluid to clean the skin. You could have a bad reaction if you are allergic to iodine. You need to inform us if you have this allergy. In this case, we use only alcohol instead. A bad reaction could cause redness, itching, rash, and/or swelling. A worse reaction could also cause fever, breathing problems, changes in pulse, convulsions, and/or fainting.

Blood Draw: Blood draws often cause mild pain, bruising, swelling, or bleeding. There is also a slight chance of infection or a small clot. If you are nervous about needles, your blood pressure and heart rate may increase for a little while. You may also feel lightheaded, sick to your stomach, or may faint. Using the same techniques used in hospitals keeps the chance of infection minimal.

Tape and sticky disks: The tape or sticky disks could cause a rash. During screening, you tell us if you are sensitive to tape. If a disk sticks very strongly, removing the disk could cause an abrasion like a rug-burn on your skin. An abrasion can feel tender or slightly painful and can increase risk of infection. If you are sensitive to tape, you may have an increased chance for abrasion. If you get an abrasion, antibiotic ointment and a sterile bandage are applied. We tell you how to take care of the site.

Medical screening: You may feel shy about giving health information. The staff collects the information in a private and professional manner. You may feel shy about being measured. You may request someone of the same sex to conduct the screening.

Initial screening form: Only members of our lab group use this form. We use the form to help decide whether you are a good candidate for the study. You may feel shy about answering questions. You may request someone of the same sex to ask you the questions. We collect the information in a private and professional manner. We keep the completed form confidential and secure.

ECG Heart Rate: This machine measures the electrical activity of your heart. You have 3 wires from the machine taped to spots on your chest. There have been no adverse effects. The tape may irritate.

Local heating: We measure the temperature of your skin under the holders. During heating, the skin

feels very warm but will not hurt. The heating makes the skin under the holder red like when you take a hot bath. The redness goes away within several hours. Some people may be more sensitive to heating. If your arm feels too hot, tell us, and we will reduce or stop the heating.

Latex: Some gloves and medical materials are made of latex rubber. You will inform us if you are allergic to latex and decline to participate in the study.

There is a risk of loss of confidentiality if your information or your identity is obtained by someone other than the investigators, 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.

WHAT ARE THE BENEFITS OF THIS STUDY?

We don't know if you will benefit from being in this study.

However, we hope that, in the future, other people might benefit from this study because this research will help us understand how blood vessels respond to Compound 21.

WILL IT COST ME ANYTHING TO BE IN THIS STUDY?

You will not have any costs for being in this research study. You/your insurance company will remain responsible for your regular clinical care.

WILL I BE PAID FOR PARTICIPATING?

You will be paid for being in this research study. You may need to provide your address if a check will be mailed to you. You will be given a parking pass for time involved at the study and screening visits.

Experimental visit: \$60 per visit (\$15/microdialysis probe + \$7.50/hour for completing the experiment)

Pro-rating: You can receive payment for experiments not completed. We will pay an amount of money equal to the part completed. For instance, if you complete half of the Experimental visit, you receive \$15.00 for each probe inserted plus \$7.50 for each hour you completed. We may ask you to repeat a trial. If you agree to repeat a trial, you receive payment for the repeated trial as stated above.

WHO IS FUNDING THIS STUDY?

This study is being funded by the National Heart, Lung, and Blood Institute (NHLBI) of the National Institutes of Health. This means that the University of Iowa is receiving payments from NHLBI to support the activities that are required to conduct the study. No one on the research team will receive a direct payment or increase in salary from NHLBI for conducting this study.

WHAT IF I AM INJURED AS A RESULT OF THIS STUDY?

- If you are injured or become ill from taking part in this study, medical treatment is available at the University of Iowa Hospitals and Clinics.
- The University of Iowa does not plan to provide free medical care or payment for treatment of any illness or injury resulting from this study unless it is the direct result of proven negligence by a University employee.

- If you experience a research-related illness or injury, you and/or your medical or hospital insurance carrier will be responsible for the cost of treatment.

WHAT ABOUT CONFIDENTIALITY?

We will keep your participation in this research study confidential to the extent permitted by law. However, it is possible that other people such as those indicated below may become aware of your participation in this study and may inspect and copy records pertaining to this research. Some of these records could contain information that personally identifies you.

- federal government regulatory agencies,
- U.S. Food and Drug Administration
- auditing departments of the University of Iowa, and the University of Iowa Institutional Review Board (a committee that reviews and approves research studies)

To help protect your confidentiality, we will limit the use and sharing of your personal research information to people who have a need to review this information. We keep the list that matches your name with your code number in a locked file or password protected file on a computer in a room that is locked when unoccupied. Only authorized members of the lab have access to the list. We label your research records with your code number and keep them in a locked file or password protected computer in a room that is locked when unoccupied. We label your research samples with your code number only.

If we write a report or article about this study or share the study data set with others, we will do so in such a way that you cannot be directly identified.

The University of Iowa Hospitals and Clinics generally requires that we document your participation in research occurring in a University of Iowa Health Care facility. This documentation will be in either your medical record or a database maintained on behalf of the institution reflecting that you are participating in this study. The information included will provide contact information for the research team as well as information about the risks associated with this study. We will keep this Informed Consent Document in our research files; it will not be placed in your medical record chart.

WILL MY HEALTH INFORMATION BE USED DURING THIS STUDY?

The Federal Health Insurance Portability and Accountability Act (HIPAA) requires University of Iowa Health Care to obtain your permission for the research team to access or create “protected health information” about you for purposes of this research study. Protected health information is information that personally identifies you and relates to your past, present, or future physical or mental health condition or care. We will access or create health information about you, as described in this document, for purposes of this research study. Once University of Iowa Health Care has disclosed your protected health information to us, it may no longer be protected by the Federal HIPAA privacy regulations, but we will continue to protect your confidentiality as described under “Confidentiality.”

We may share your health information related to this study with other parties including federal government regulatory agencies, the University of Iowa Institutional Review Boards and support staff, and the U.S. Food and Drug Administration.

You cannot participate in this study unless you permit us to use your protected health information. If you choose *not* to allow us to use your protected health information, we will discuss any non-research

alternatives available to you. Your decision will not affect your right to medical care that is not research related. Your signature on this Consent Document authorizes University of Iowa Health Care to give us permission to use or create health information about you.

Although you may not be allowed to see study information until after this study is over, you may be given access to your health care records by contacting your health care provider. Your permission for us to access or create protected health information about you for purposes of this study has no expiration date. You may withdraw your permission for us to use your health information for this research study by sending a written notice to: [REDACTED]

[REDACTED]. However, we may still use your health information that was collected before withdrawing your permission. Also, if we have sent your health information to a third party, such as the study sponsor, or we have removed your identifying information, it may not be possible to prevent its future use. You will receive a copy of this signed document.

IS BEING IN THIS STUDY VOLUNTARY?

Taking part in this research study is completely voluntary. You may choose not to take part at all. If you decide to be in this study, you may stop participating at any time. If you decide not to be in this study, or if you stop participating at any time, you won't be penalized or lose any benefits for which you otherwise qualify.

Will I Receive New Information About the Study while Participating?

If we obtain any new information during this study that might affect your willingness to continue participating in the study, we'll promptly provide you with that information.

Can Someone Else End my Participation in this Study?

Under certain circumstances, the researchers might decide to end your participation in this research study earlier than planned. This might happen if you become pregnant, if the researcher decides to end the study early, or if for any reason the researcher decides that it is no longer safe for you to continue.

WHAT IF I HAVE QUESTIONS?

We encourage you to ask questions. If you have any questions about the research study itself, please contact: [REDACTED] If you experience a research-related injury, please contact: [REDACTED]

If you have questions, concerns, or complaints about your rights as a research subject or about research related injury, please contact the Human Subjects Office, 105 Hardin Library for the Health Sciences, 600 Newton Rd, The University of Iowa, Iowa City, IA 52242-1098, (319) 335-6564, or e-mail irb@uiowa.edu. General information about being a research subject can be found by clicking "Info for Public" on the Human Subjects Office web site, <http://hso.research.uiowa.edu/>. To offer input about your experiences as a research subject or to speak to someone other than the research staff, call the Human Subjects Office at the number above.

This Informed Consent Document is not a contract. It is a written explanation of what will happen during the study if you decide to participate. You are not waiving any legal rights by signing this Informed Consent Document. Your signature indicates that this research study has been explained to you, that your questions have been answered, and that you agree to take part in this study. You will

receive a copy of this form.

Subject's Name (printed): _____

(Signature of Subject)

(Date)

Statement of Person Who Obtained Consent

I have discussed the above points with the subject or, where appropriate, with the subject's legally authorized representative. It is my opinion that the subject understands the risks, benefits, and procedures involved with participation in this research study.

(Signature of Person who Obtained Consent)

(Date)