Sex Differences in Cerebral Blood Flow during High Oxygen Breathing

NCT05958303

9/12/2024

University of Wisconsin-Madison
Consent to Participate in Research
and
Authorization to Use Protected Health Information for Research

Study Title for Participants: Sex Differences in Cerebral Blood Flow during High Oxygen Breathing

Formal Study Title: Human cerebral blood flow regulation: sex, mechanism, and stress differences

Principal Investigator: William G. Schrage, Ph.D. (phone: 608-262-7715)

Co-Principal Investigator: Marlowe W. Eldridge, MD.

Where Lead Researcher Works: University of Wisconsin-Madison; Department of Kinesiology; 1300 University Ave; Madison, WI 53706

Invitation

We invite you to take part in a research study examining the control of brain blood flow. You are invited to take part because you are between 18 and 40 years old and generally healthy. Approximately 30 individuals will participate in this study.

The purpose of this consent form is to give you the information you need to decide whether to be in the study. It also explains how health information will be used for this study and for other research in the future and requests your authorization (permission) to use your health information. Ask questions about anything in this form that is not clear. If you want to talk to your family and friends before making your decision, you can. When we have answered all your questions, you can decide if you want to be in the study. This process is called “informed consent.”

Why are researchers doing this study?

The purpose of this study is to test brain blood flow responses when the body is challenged by stressors. We want to know: 1) whether and how males and females differ in control of brain blood flow, 2) whether males and females differ in brain blood flow responses to breathing more oxygen (hyperoxia). We will test if males and females respond differently and how they respond differently. Funding for this study is provided by the National Institute of Health (NIH).

What will my participation involve?

If you decide to participate in this research study you may be asked to come in for up to four separate visits: a screening visit (~1hour), exercise screening visit (30-45 minutes), AND two study visits (~2-2.5 hours each). These two study visits are considered visit A and visit B and are described below.

Note that you may be asked to come back for an additional screening visit in the event that we are unable to obtain a blood sample or technical difficulties occur during the initial screening visit.

What will happen in this study?

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Screening Visit (~1 hour): The screening procedures are described below. After you complete the screening, you may be enrolled in the study if you qualify.

1. Documentation: After providing informed consent, you will be asked to fill out several forms/questionnaires. This includes medical history, demographics, MRI safety form, and medication form. You may skip any question on the questionnaire that you do not wish to answer.
2. Anthropometric (Body) Measurements: We will measure height, weight, waist and hip circumference, and blood pressure.
3. Urine Pregnancy Test (Females only): Female subjects will be **required** to have a negative urine pregnancy test which will be reviewed and confirmed by research staff.
4. Venipuncture: Blood will be drawn from a vein in your arm by a trained and certified person. You will have a total of up to 1 tablespoon or 20mL taken from you. This blood will be used to test for circulating substances in your blood such as sugar, cholesterol, and fats.

Exercise Visit (<1 hour):

Maximal Aerobic fitness test (VO_2): This test is used to measure your fitness. You will complete a maximal exercise test on a treadmill. You will wear a heart rate monitor (Polar Heart Rate Monitor), and mouthpiece or mask that will capture your breath but will allow you to breathe normally. This test increases in difficulty over time, but usually only lasts 812 minutes for most people.

The tests start at 5mph and 3% incline and increases 1mph and 1% incline every 2 minutes.

Pre-Study Visit Procedures: Specific pre-visit procedures to be followed are outlined below:

1. Fasting: You will fast for a minimum of 8 hours prior to the study visits. Plain drinking water is allowed.
2. Withholding exercise, caffeine and NSAIDs; We ask that you refrain from vigorous exercise for 24 hours, and refrain from caffeine and NSAIDs like Ibuprofen for at least 24 hours prior to the study visits. You may and should drink water as normal.
3. For females only: If you are currently taking hormonal birth control for contraception (e.g. the Pill, patch, or ring), you will need to temporarily stop taking these medicines while you are in the study. This time may last from 1-6 months (depending on MRI visits-see below). You will need to be off hormonal birth control for at least one menstrual cycle before Study Visit
4. If you are unwilling or unable to stop birth control, you will not be eligible to participate in this study. An endocrinologist who specializes in these medicines will work with you and the study team to make a plan to temporarily stop birth control and complete the study visits.

Study Visit Procedures (Study Visits)

1. Urine Pregnancy Test (Females only): Female subjects will be **required** to have a negative urine pregnancy test on the day of the study visit, which will be reviewed and confirmed by research staff.
2. Measurements: Heart rate will be monitored by electrocardiogram (ECG) or by pulse oximeter on your fingertip. Blood pressure will be monitored by a cuff on your upper arm similar to clinics. Blood oxygen will be measured with a pulse oximeter on your fingertip; your breathing will be measured using a breathing mask.

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3. Intravenous (IV) Catheterization: A highly trained person will place a catheter in a forearm vein. This catheter is used for blood sampling. If the blood sampling cannot be obtained or completed, it is not a requirement to continue with other study procedures.
4. Blood Sampling: Blood will be drawn from the arm catheter (up to 10 tablespoons; ~150 mL) to test for blood values (sugar, cholesterol, hormones, etc.) and other research values. Most of these are research values and not clinical values (such as lab tests you would get at a doctor's office or hospital visit), so we are not allowed to share this information with you.
5. Magnetic Resonance Imaging (MRI): An MRI is a medical imaging technique used to visualize detailed images of internal structures. We are using it to collect images of your brain blood vessels and measure brain blood flow. The scanner looks like a large hollow tube. You will lie flat on your back on a moveable table. The table will slide inside the scanner to take measurements at baseline while breathing room air and during hyperoxia. Scans (see figure below) taken during study visits will typically last around 4-6 minutes each, but you will remain in the scanner between scans as well. Total time in the scanner will be about 60 minutes per visit.
6. Functional Magnetic Resonance Imaging (fMRI): fMRI scans will be collected while you are in the scanner to identify the brain regions engaged during task performance and to assess how these responses correlate with CBF. fMRI tasks will include a verbal fluency task and a rotating checkerboard task. The verbal fluency task involves presenting a letter to the subject and asking them to generate words starting with that letter. The visual task involves the subject looking at a green dot in the center of a rotating checkerboard. These tasks will also involve other equipment, such as a visual system.
7. High Oxygen (Hyperoxia): While you are in the MRI scanner, you will breathe in air through a mask over your mouth/nose that has higher amounts of oxygen than room air (100% vs. 21%). You will breathe this air for ~30-45 minutes. and remain in the scanner while we complete other steps of the study visit.
8. Supplementation:
    a) At the MRI study visits, you will receive either antioxidant or placebo pills. You will receive 2 doses of either just placebo or just antioxidants during the first study visit, and then you will receive the other during your second study visit. This study is blinded; meaning neither you nor the researchers will know whether you received the antioxidant or the placebo.
    b) During the MRI study visits, you will orally ingest either antioxidant or a placebo pills at the start of the visit. You will then orally ingest a second dose of either antioxidants or placebo 30-60 minutes after the first dose.
    c) Antioxidants (vitamin C, vitamin E, alpha lipoic acid (ALA): These antioxidants are over-the-counter supplements you can find in any drug store. They are generally believed to neutralize compounds in the body called free radicals that can be harmful in large quantities. We are administering the antioxidants to counteract these free radicals and see what that does to brain blood flow.
    d) Placebo: Placebo is substitute for the active treatment. There are no active ingredients or properties in the placebo.

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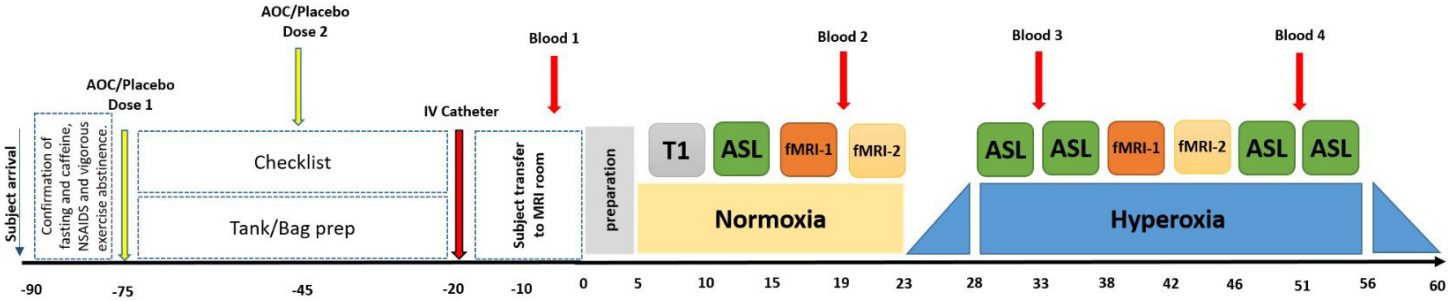

Protected health information (PHI) used in this study:

Protected health information, also called PHI, is information about your physical or mental health that includes your name or other information that can identify you, like your date of birth or medical record number. To do this study, we will use the following kinds of PHI:

Results of tests or procedures done as part of the study Things you tell the researchers about your health

How long will I be in this study?

Your participation will last ~1 hour for the screening visit, ~45 min for the exercise visit, and ~2 hours each for the MRI study visits (~3-4 hours total). After screening, we will try to schedule your 2 study visits in the same week, although these visits can happen over a 6-month period. After each MRI study visit, we will follow-up with you by telephone approximately 24 hours after the visit to make sure you are feeling well.

The researchers may take you out of the study, even if you want to continue, if

- your health changes and the study is no longer in your best interest
- you do not follow the study rules or no longer meet the requirements to be in the study ● the study is stopped by the sponsor or researchers

Do I have to be in the study? What if I say "yes" now and change my mind later?

No, you do not have to be in this study. Taking part in research is voluntary. This means that you decide if you want to be in the study. If you decide now to take part, you can choose to leave the study at any time. You can ask all the questions you want before you decide. If you stop being in the research, already collected data may not be removed from the study database. You may be asked whether the investigator can collect data from your routine medical care. If you agree, this data will be handled the same as research data.

If you decide to be in the study, the researchers will tell you about new information or changes in the study that may affect your willingness to continue in the study. Let the researchers know if you choose to leave the study. If you decide not to take part in the study, or if you choose to leave the study, your choice will not affect any treatment relationship you have with healthcare providers at UW-Madison, UW Health or any affiliated organizations, or any services you receive from them. No matter what decision you make, and even if your decision changes, there will be no penalty to you. You will not lose medical care or any legal rights.

Your authorization for researchers to use your protected health information (PHI) will last until the research study is done. However:

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- You can choose to take back your authorization for researchers to use your health information. You can do this at any time before or during your participation in the research.
- If you take back your authorization, information that was already collected may still be used and shared with others, but the researchers will no longer be able to collect NEW information about you.
- If you take back your authorization, you will not be able to take part in the research study.
- To take back your authorization, you will need to tell the researchers by writing to the Lead Researcher, William G. Schrage, Ph.D., at University of Wisconsin-Madison, Department of Kinesiology, 1300 University Ave, Madison, WI 53706.

Will being in this study help me in any way?

Being in this study will not help you directly. But your participation in the study may benefit other people in the future by helping us learn more about how males and females regulate brain blood flow differently.

How is being in this study different from my regular health care?

This study is not part of your health care.

Will I receive the results of research tests?

Most of the tests that are part of this study are for research purposes only. Because of this, we will not tell you or your doctors the results of these research tests.

MRI Scans: Whenever an MRI of the brain is done, there is the chance of finding something unexpected. There may be benefits to learning such results (such as early detection and treatment of a medical condition), but there are risks as well (such as problems with getting insurance or a job, or feeling worried about a finding for which no treatment is required or appropriate). The MRI we are using in this research study is not the same quality as an MRI that you may have as part of your health care. The images from the MRI will not be reviewed by a physician who normally reads such images (such as a neuroradiologist). As a result, you will not be informed of any unexpected findings. The results of your MRI will not be placed in your medical record. If you believe you are having symptoms that may require clinical imaging, you should contact your primary care physician.

Some of the MRI data will be acquired using investigational software and hardware in addition to the standard MRI technology. The investigational software and hardware enable newly developed features that are not yet FDA approved for clinical use. Although not approved by the FDA, the system is being operated under the FDA safety specifications.

What are the risks?

Study procedures and the associated risks are described below.

1. **Fasting:** Fasting can make you feel hungry, irritable, light-headed, and/or tired. There are no long-term effects of fasting. If you feel dizzy or nauseous stop the fast and contact the research team.
2. **Urine Pregnancy Test** (females only): There are no risks associated with a urine pregnancy test.

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3. **Venous Blood Sample:** Blood sampling from a vein poses very little risk to subjects. There is a small chance that drawing your blood will be painful or will cause bleeding, infection (less than 1%), fainting, or dizziness. We will minimize the chances of these risks by drawing blood while you are lying down and by using only trained personnel.
4. **Maximal Exercise (fitness) Test:** The maximal exercise test may leave you with feelings of exertion, fatigue, and breathlessness. You may feel some discomfort due to the monitoring equipment (e.g. mouthpiece or mask). Serious complications including orthopedic injury, myocardial infarction (heart attack), arrhythmia (abnormal heart rate), hemodynamic instability (blood pressure changes), and death are rare.
5. **Temporarily stopping hormonal birth control (some females only)**: The biggest risk of stopping birth control is the risk of pregnancy. If you are sexually active and are stopping your hormonal birth control, you will need to use a backup method of birth control such as condoms or abstinence. If you were to become pregnant, you would need to notify the study team. Pregnant females cannot participate in the study.

   Additional risks of stopping birth control may depend on the reasons that you may have started birth control. Your periods will return to what they were like before starting birth control. This means that for some females they will not notice a change but for other females their periods could get heavier, more painful, or more irregular and they may notice worsening of menstrual symptoms such as bloating, mood swings, or headaches.

   If you feel any side effects are not tolerable and you want to restart your birth control, that is your choice. However, you must tell the study team, as you will need to stop participating in this study.

6. **Magnetic Resonance Imaging:** Before your scan, you will be asked a series of medical history questions to make sure you are safe to go into the scanner. The MRI scanner uses a powerful magnetic field to create images of the body. Some people should not participate in MRI studies. These include persons with shrapnel or certain metallic implants, such as prostheses, aneurysm clips, or persons with electronic implants, such as cardiac pacemakers or implanted hearing devices. The magnetic field generated by the MR machine can cause displacement or malfunctioning of these devices. Females who are pregnant should not participate in MR studies. The potential risks to a fetus are not known.
   Some people report anxiety or claustrophobia in the MR scanner since the head must be placed fully inside the scanner tube. If anxiety or claustrophobia occurs, please let us know and we will stop the scan and bring you out of the scanner. In addition, fatigue and physical discomfort are possible. The MRI scanner makes a great deal of noise when taking images. To minimize the level of noise, you will be fitted with disposable earplugs or headphones to wear during the procedure. These may be a bit uncomfortable to wear and will not eliminate all sound so that communication with you is still possible. fMRI cognitive tasks performed in the scanner by the subjects, could cause discomfort due to the visual system required by the subjects. Performing the cognitive task themselves could led to subject fatigue.
7. **Lying down**: You will be asked to lie down for 1-2 hours. This might make you feel tired, stiff, and/or bored. There are no known long or short-term risks for lying down for 1-2 hours.
8. **IV Catheter:** Risks of placing an IV catheter in the arm include bruise or clot formation and infection. However, a qualified person will place the IV catheter and will take precautions to avoid bruising. Minor risks may be: pain at the site of catheter insertion, bruising after we

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remove the catheter and soreness over the site. These should all be short-lived and will decrease after several days. Serious complications are unlikely.

9. **High Oxygen (Hyperoxia):** Hyperoxia exposure will last approximately 30 minutes in total but may be increased to 45 minutes to obtain all research data. Short-term exposure to breathing air high in oxygen may cause constriction in blood vessels and, therefore, reduced blood flow, but has no known risks during the brief period used here. This trial will be performed while lying down, minimizing the risk of injury. If this procedure makes you feel too uncomfortable, you can stop at any time.
10. **Antioxidant supplements:** Each of the antioxidant pills used in this protocol are sold over the counter in the US with excellent safety/tolerability. Side effects of these supplements are rare, but may include diarrhea, nausea, vomiting, abdominal cramps/pain, heartburn, tiredness, dizziness, or headache. When these occur, however, it is typically due to taking them repeatedly over a long period of time. With our study, you will only take these supplements on one of the study visits. You will be monitored continuously for any side effects.
11. **Breach of Confidentiality:** There is a risk that your information could become known to someone not involved in this study.

Will being in this study cost me anything?

There will be no cost to you for any of the study activities or procedures. If you need treatment for side effects while you are on the study, you or your insurance will need to pay for this treatment.

Will I be paid or receive anything for being in this study?

Visit or procedure	Payment amount
Screening Visit	$20
Exercise Visit	$20
MRI study visits	$30/per hour; rounded to the next half hour
Completing both MRI study visits	Bonus $30
If you complete all procedures and visits	~$190-220 total

If a rescreening visit is required, you will be paid the same amount as for the initial screening visit ($20). Payment will be provided at the end of the study. If you choose to leave early or we take you off the study for any reason, you will receive a pro-rated amount based on the total number of hours in which you participated in the study visit.

What happens if I am injured or get sick because of this study?

If you are injured or get sick because of this study, medical care is available to you through UW Health, your local provider, or emergency services, as it is to all sick or injured people.

If it is an emergency, call 911 right away or go to the emergency room.

For non-emergency medical problems, contact the study team for instructions.

Call the Lead Researcher, William G. Schrage, Ph.D., at 608-262-7715 to report your sickness or injury.

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Here are some things you need to know if you get sick or are injured because of this research:

- If the sickness or injury requires medical care, the costs for the care will be billed to you or your insurance, just like any other medical costs.
- Your health insurance company may or may not pay for this care.
- No other compensation (such as lost wages or damages) is usually available.
- UW-Madison and UW Health do not have a program to pay you if you get sick or are injured because of this study.
- By signing this consent form and taking part in this study, you are not giving up any legal rights you may have. You keep your legal rights to seek payment for care required because of a sickness or injury resulting from this study.

How will the researchers keep my research information confidential?

We have strict rules to protect your personal information and protected health information (PHI). We will limit the use and disclosure of your personal information, including research study and medical records, to people who have a need to review this information. The study is protected by a Certificate of Confidentiality from the National Institutes of Health. This means that even if the police or courts ask to look at the data we have collected, we will not share any information that would identify you as a participant in the study. We may publish and present what we learn from this study, but none of this information will identify you directly without your permission.

However, we cannot promise complete confidentiality. Federal or state laws may permit or require us to show information to university or government officials and to study sponsors responsible for monitoring this study. This includes University of Wisconsin and its representatives and affiliates, including those responsible for monitoring or ensuring compliance, such as the Human Research Protection Program, the Food and Drug Administration, and the Department of Health and Human Services. By signing this consent form, you are authorizing this access.

We may also have to tell appropriate authorities, such as child protective services or health care providers, if we learn during the study that you or others are at risk of harm (for example, due to child or elder abuse, or suicidal thoughts).

Authorizing the research team to use your PHI means that we can release it to the people or groups listed below for the purposes described in this form. Once your health information is released outside UW-Madison or UW Health it may not be protected by privacy laws and might be shared with others. Also, with appropriate institutional permissions and confidentiality protections, we might use information and biospecimens that we collect during this study for other research or share with other researchers without additional consent or authorization from you or your legally authorized representative.

A description of this clinical trial 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.

Will information from this study go in my medical record?

A medical record may be created for you if you do not already have one. Your medical record might say that you participated in this study, and a copy of this consent and authorization form might go in your medical record. None of the information we collect for this study will go in your medical record.

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What will happen to my data and biospecimens after my participation ends?

This study is collecting data and samples from you. We would like to make your data and samples available for other research studies that may be done in the future. The research may be about similar diseases or conditions to this study. However, research could also be about unrelated diseases, conditions, or other types of research. These studies may be done by researchers at this institution or other institutions, including commercial entities. Your data and samples may be shared with researchers around the world. Our goal is to make more research possible. We plan to keep your data and samples for an indefinite period of time. If you wish to withdraw your permission to bank data/specimens you will need to send Dr. Schrage a letter indicating your reason for withdrawal, then your data/specimens will be destroyed and deleted from our storage. To get your data or samples, future researchers must seek approval from this institution and review by an IRB may be required.

We will protect the confidentiality of your information to the extent possible. Your data and samples will be coded to protect your identity before they are shared with other researchers. Only the study team will have a code key that can be used to link to your identifying information. The code key will be securely stored.

We will do our best to protect your data and samples during storage and when they are shared. However, there remains a possibility that someone could identify you. There is also the possibility that people who are not supposed to might access your data and samples. In either case, we cannot reduce the risk to zero.

Participating in this study means you agree to share your data and samples. You can change your mind later, but researchers might still use your data and samples if they have already been shared. If you do not want your data and samples used for other research studies, you should not participate in this study.

How long will my permission to use my health information last?

By signing this form, you are giving permission for your health information to be used by and shared with the individuals, companies, or institutions described in this form. Unless you withdraw your permission in writing to stop the use of your health information, there is no end date for its use for this research study. You may withdraw your permission at any time by writing to William G. Schrage, Ph.D., University of Wisconsin-Madison, Department of Kinesiology, 1300 University Ave, Madison, WI 53706.

Beginning on the date you withdraw your permission, no new information about you will be used. Any information that was shared before you withdrew your permission will continue to be used. If you withdraw your permission, you can no longer actively take part in this research study.

Use of email

We are requesting your email address so we can schedule study visits and send out study visit reminders. Email is generally not a secure way to communicate about your health as there are many ways for unauthorized users to access email. You should avoid sending sensitive, detailed personal information by email. Email should also not be used to convey information of an urgent nature. If you need to talk to someone immediately, please contact William G. Schrage, Ph.D. at (608) 262-7715.

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You do not have to provide your email address to participate in this study.

What if I have questions?

If you have questions about this research, please contact the Lead Researcher, William G. Schrage, Ph.D., at 608-262-7715

If you have any questions about your rights as a research participant or have complaints about the research study or study team, call the confidential research compliance line at 1-833-652-2506. Staff will work with you to address concerns about research participation and assist in resolving problems.

Agreement to participate in the research study

You do not have to sign this form. If you refuse to sign, however, you cannot take part in this research study.

If you sign the line below, it means that:

- You have read this consent and authorization form.
- You have had a chance to ask questions about the research study, and the researchers have answered your questions.
- You want to be in this study.
- You give authorization for your protected health information to be used and shared as described in this form.

_____

Printed Name of Participant

_____

Signature of Research Participant Date

_____

Signature of Person Obtaining Consent and Authorization Date

Time: ☐☐ **:** ☐☐ (using 24-hour format)

****You will receive a copy of this form****

Applicable to females only:

☐ **I do not currently take hormonal birth control and do not intend to start during this study**

☐ **I am currently taking hormonal birth control and consent to stopping while participating in this study**

This study is considered Phase 3 of a larger study. We would like your permission to contact you about participation in Phases 1 & 2. The study team will need to determine if you are eligible for Phases 1 & 2. The phase 3 activities are very similar to the Phases 1 & 2 study activities. We will explain this in more detail if you agree to be contacted about Phases 1 & 2.

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☐ **Yes, you may contact me about participation in Phases 1 & 2.**

☐ **No, I do not want to be contacted about participation in Phases 1 & 2.**

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