U.S. Army Research Institute of Environmental Medicine

CONSENT TO PARTICIPATE IN RESEARCH

Title of Protocol: Influence of caffeine on psychomotor vigilance and carbon dioxide tolerance during graded hypercapnia

Principal Investigator: Benjamin Ryan, Ph.D.

Introduction: You are being asked to participate in this research study because you are age 18-45, healthy and physically fit. You do not have to take part in this research. It is your choice.

The table below summarizes some **key** points to think about. After reading this summary, if you think you might be interested in participating, read the rest of the consent form for more details about the study.

RESEARCH SUMMARY	
Informed Consent	It is important that you understand this research study so that you can make an informed decision. This process is called informed consent. • Please ask questions about anything you do not understand. • Feel free to talk with your family, friends, or others before you decide. • After your questions have been answered, you will be asked if you want to participate. If you agree, you will sign this consent form. • You will be given a copy of this form to keep.
Voluntary Participation	You do not have to take part in this research. It is your choice. You can also choose to stop participating at any time during the study.
Purpose	This study will determine if caffeine can help reduce the negative effects of breathing increased levels of carbon dioxide.
Duration	You will be in this study for 4 visits (1 hour to 2.5 hours each) over the course of ~2-4 weeks (grand total of 7.5 hours).
Procedures	While you are in the study, you will: • Breathe **elevated** levels of carbon dioxide (0%, 2%, 4%, 6%, and 8%) with **normal** levels of oxygen in stages for **12** minutes each (total of **4** times over the course of the study). • Ingest capsules containing caffeine (400 mg; this is a **high** dose) or placebo (no caffeine) • Perform 5-minute tests to assess attention and reaction-time many times. • Fill out surveys several times to measure things like breathing difficulty, overall discomfort, headache, and mood • Provide a urine sample on testing days

	• Have blood samples collected from your arm (total of **3** times over the course of the study) and finger (total of **15** times over the course of the study) During the study, you will be asked to meet the following requirements: • **No** exercise or alcohol 24 hours before each visit. • **No** caffeine in the 12 hours before study visits. • **No** caffeine in the 12 hours after visits 3-5. • **No** food/beverage (other than water) after lights out and remain fasted until next day after testing on each visit (~10 hours).
Risks	The **main** risks from being in this study are: • Breathing gas with elevated levels of carbon dioxide (CO_2) (feeling out of breath, panic, headache, stomach upset, lightheadedness, fatigue, rapid/strong heartbeat, fainting) • Side effects of caffeine (restlessness, jitteriness, shakiness, headache, dizziness, rapid heart rate, anxiety, stomach upset, low blood sugar, difficulty sleeping) • Blood collection (minor discomfort, infection, fainting) Steps to lessen the risks are described later in this consent form.
Benefits	There is no direct benefit to you for participating in the study. Information from this study may benefit warfighters and other people in the future.
Payment	You will be paid for your participation in this study.
COVID-19 risk mitigation	Study staff and volunteers will comply with all COVID-19 risk mitigation procedures in place at USARIEM during the time of data collection. As such, volunteers may be asked to wear face masks and use hand sanitizer during data collection activities (in accordance with prevailing recommendations at the time of data collection) and may be asked to wear gloves (i.e., nitrile gloves) during data collection activities. You also may be asked to undergo COVID-19 testing prior to each visit.

WHY IS THIS RESEARCH BEING DONE?

The purpose of this research is to determine the effect of caffeine on attention, reaction-time, and tolerance while breathing different amounts of CO_2 (0%, 2% 4%, 6%, and 8%).

An increase in the amount of CO_2 in the air has been identified as an important environmental stress that Warfighters may encounter while operating in subterranean (underground) or enclosed spaces. This is an experimental study designed to determine if caffeine can help reduce the negative effects of breathing increased levels of CO_2 on cognitive performance and improve CO_2 tolerance.

WHAT WILL HAPPEN DURING THIS RESEARCH?

If you agree to participate in this research, you will be asked to do the following:

You will first need to be cleared by our Office of Medical Support and Oversight (OMSO) at United States Army Research Institute of Environmental Medicine (USARIEM) to make sure you are in good health. This will consist of 1 or 2 days (~1 hour each) in which the medical staff will have you provide urine and blood samples, as well as complete a physical. If you are cleared to participate in this study, you will complete 4 visits of ~1 to 2.5 hours duration each at our lab over a period of ~2-4 weeks (**See Table 1**) for total ~ 7.5 hours. All visits will occur at USARIEM.

Table 1. Overview of study visits

Study Phase	Duration / Activities
Medical Screening	**1 or 2 Days, 1 hour**
	• Medical Screening • Urine and blood sample • Physical exam
Visit 1	**1 Day, 1 hour**
	• Height and Weight Measurement • Heart rate and Breathing Measurement Familiarization • Attention and Reaction Time Test Familiarization • Surveys
Visit 2	**1 Day, 1.5 hours**
	• Weight Measurement • Urine Sample • Blood samples (1 from arm vein, 5 from fingertip) • Breathe elevated levels of carbon dioxide (CO_2) • Heart rate, Blood Pressure, and Breathing Measurements • Attention and Reaction Time Testing • Surveys
Visits 3 and 4	**1 Day, 2.5 hours each**
	• Weight Measurement • Urine Sample • Take caffeine (400 mg) or placebo (no caffeine) capsules • Breathe elevated levels of carbon dioxide (CO_2) • Blood samples (1 from arm vein, 5 from fingertip) • Heart rate, Blood Pressure, and Breathing Measurements • Attention and Reaction Time Testing • Surveys

Visit 1 (Familiarization)

When you arrive to the lab after an overnight fast (~10 hours), we will begin by taking your height and weight. You will be provided a small breakfast to eat. Please inform us if you have any dietary restrictions or food allergies. You will be provided with the instruction for the 5-minute psychomotor vigilance test (PVT). PVT is a computerized test that measures attention and reaction-time, you will be asked to react to signals on a screen by pressing a button. See Figure 1 for a screenshot of the PVT. You will be also provided instructions on surveys for

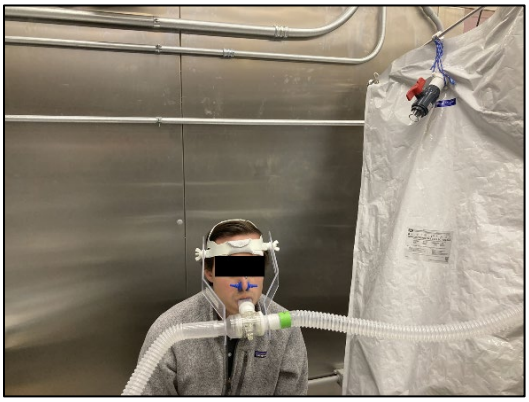
breathing difficulty, discomfort, headache, and mood. You will respond to these by pointing to a number or with a pencil.

You'll then be fitted for a heart rate monitor, mouthpiece, and nose clip that will be used during the testing visits. The mouthpiece does not restrict your breathing. See Figure 2 for a picture of the mouthpiece and nose-clip.

While breathing room air through mouthpiece/nose clip, you will practice the PVT and surveys in the seated position at least 3 times. At the end of the visit, you will fill out questionnaires on your regular caffeine intake, and if you are female, a questionnaire on menstrual history. We will also provide you a 24-hour diet log to record your diet the day before visit 2 and to be used for subsequent study visits.

Figure 1. Screenshot of Psychomotor Vigilance Test (PVT)

Figure 2. Experimental Testing Set-up



Visits 2-4 (Testing)

Caffeine Dosing:

During visit 2, you will not be given any capsules. During visits 3 and 4, you will be given capsules containing 0mg or 400mg of caffeine. For context, one 8-ounce cup of coffee contains ~100mg caffeine, so the 400mg caffeine dose contains a similar amount of caffeine to 4 cups of coffee. The amount of caffeine you will be given on each testing day will not occur in any particular order. Neither you nor the research staff involved in testing will know what amount of caffeine you have been given. However, other members of the study staff that are not involved in testing and the OMSO will know what dose of caffeine you received.

Diet, hydration, activity, and sleep opportunity standardization:

To prepare for the visits, we will ask you to maintain the dietary pattern recorded on the 24-hour diet log and abstain from exercise for the 24 hours prior to each visit. The night before your visits, you should have 7 hour sleep opportunity (e.g., lights out 2300-0600 hrs) and drink an extra 0.5 L of water (between 1800-2200 hrs), you are not allowed to have any food/beverage other than water after lights out the until completion of the visit next day (~10h).

Testing Days:

For each visit, you will arrive to the lab with your first morning void urine sample (collection cup provided). Before the testing, we will measure your weight and will use the urine sample to determine if you are sufficiently hydrated. If you are female, we will perform a pregnancy test using the same urine sample, you cannot continue with the study if the result is positive. You will be provided a small breakfast to eat.

Figure 3 below shows an overview of the testing timeline. All testing will be done in seated position.

We will take a blood sample from a vein in your arm 10 minutes before starting the test; for visit 3-4, the blood draw comes after you take the caffeine/placebo capsule and rest for 50 minutes.

You will then put on a heart rate monitor and mouthpiece/nose clip to measure the oxygen and CO_2 you breathe out. While wearing the mouthpiece/nose clip, you will breathe a gas mixture from a large bag connected by a tube (see Fig 2 above). The gas mixture will always contain normal levels of oxygen (21%), and the level of CO_2 will be gradually increased every 12 minutes (from 0 - 12 minutes, 0% CO_2 (similar to normal room air); from 12 - 24 minutes, 2%

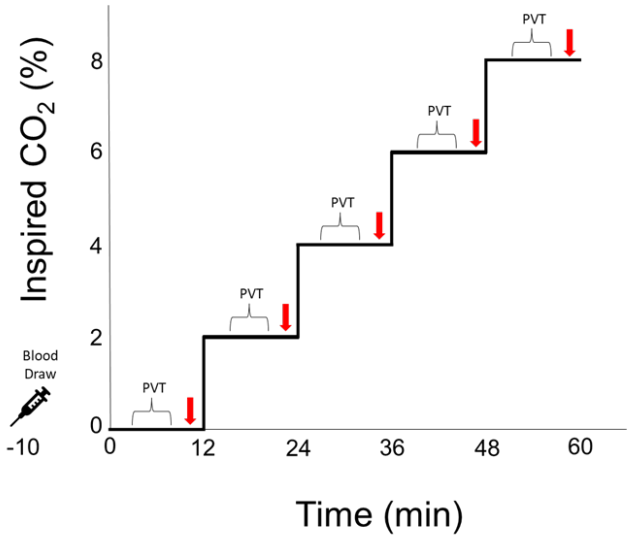
CO_2; from 24 - 36 minutes, 4% CO_2; from 36 - 48 minutes, 6% CO_2; from 48 to 60 minutes, 8% CO_2).

During each 12-minute stage of the test, you will start the 5-minute PVT at minute 2 of each stage. After completing each PVT, we will measure your blood pressure and collect a fingerstick blood sample (less than ¼ teaspoon per fingerstick). You will then be asked to complete surveys about your breathing difficulty, overall discomfort, headache, and mood. Your heart rate will be monitored continuously throughout the test.

The total time breathing through the mouthpiece/nose clip will be ~60 minutes. You can end the testing at any time if you develop discomfort and want to stop. We will be monitoring the levels of CO_2 you are breathing out and may end the test before completion to make sure the CO_2 levels in your body do not become too high. Immediately after the test ends, you will return to breathing room air.

At the end of visits 3-4, you will complete a survey to indicate if you believe you received a capsule containing 400mg caffeine or placebo.

Figure 3. Overview of Testing Timeline. PVT indicates the Psychomotor Vigilance Test that will begin at the second minute of each stage. Red arrows indicate measurements taken during each stage that include blood pressure, a fingerstick, and ratings of discomfort, headache, mood, and breathing difficulty.



HOW LONG WILL I BE IN THE STUDY?

Testing will occur over the course of 2-4 weeks with 5 total visits of 1-2.5 hour duration per visit (grand total of ~7.5 hours over the course of the study).

WHAT PRECAUTIONS DO I NEED TO TAKE?

- No exercise or alcohol in the 24 hours before each study visit.
- No caffeine for 12 hours prior to all study visits and for 12 hours after visits 3-5.

- No food/beverage (other than water) after lights out and remain fasted until next day after testing on each visit (~10 hours).

HOW MANY PEOPLE WILL BE IN THE STUDY?

Up to 48 volunteers may consent to this study, but the researchers only need complete data from 12 male and 12 female volunteers to finish the study. All screening and enrollment will stop once complete data has been collected from 12 male and 12 female volunteers. Although you may consent and desire to participate in this study, if the investigators are able to get enough data from past subjects, then you may not be tested and your participation will end.

WHAT ARE THE POSSIBLE RISKS AND DISCOMFORTS?

Source of Risk	Risk(s)	How We Will Minimize
Breathing elevated levels of CO_2	Headache Feeling out of breath Stomach upset Lightheadedness Fatigue Fainting Sweating Rapid/strong heartbeat Fetus/embryo risks unknown	• You are a healthy and will be medically screened by the Office of Medical Support and Oversight • Study staff will be monitoring you throughout testing • You will be able to immediately stop breathing the gas mixture if your symptoms become intolerable • Pregnant individuals will be excluded from participation
Caffeine supplementation	Restlessness and shakiness Headache Dizziness Rapid heart rate Anxiety Stomach upset Difficulty sleeping	• You are a healthy and will be medically screened by the Office of Medical Support and Oversight • no caffeine 12 hours before and after each trial
Heart rate/blood pressure monitoring	Skin irritation/chaffing	• Study staff will monitor your skin for irritation • Medical staff is available to treat you in the event of skin irritation
Blood collection	Pain, bruising, infection, swelling at puncture site, dizziness, fainting, nausea, vomiting	• Only performed by credentialed staff • Puncture site cleaned with disinfectant • You will be seated

WHAT ARE THE POSSIBLE BENEFITS FROM BEING IN THIS RESEARCH?

There are no direct benefits from you participating in this research study. Information gathered from this research may benefit warfighters and other people in the future.

WHAT IF UNEXPECTED INFORMATION IS LEARNED ABOUT MY HEALTH?

If any unexpected health information is found during your participation, the Principal Investigator (PI) will direct you to OMSO (for military individuals) or your primary care physician (PCP; for civilian individuals). No diagnoses will be made by study staff; therefore, no findings will be reported to PCP or authorities.

WILL RESEARCH RESULTS BE SHARED WITH ME?

After completion of the overall study (all participants), we will be able to share your caffeine dose order and overall study findings upon request.

WHAT ARE MY OTHER OPTIONS IF I DO NOT PARTICIPATE IN THIS STUDY?

The only alternative is to not participate in the study.

WILL I HAVE TO PAY FOR ANYTHING IF I TAKE PART IN THIS RESEARCH?

There are no anticipated costs for this study. We will not reimburse a participant for expenses paid (travel, etc.) in order to allow an individual to participate in the study.

WILL I BE PAID TO TAKE PART IN THIS RESEARCH?

Participants will receive $45.00 per blood collection. There are a total of 18 blood collections so individuals who complete the study will receive a total of $810. No compensation will be offered for the blood draw performed by OMSO as part of the medical clearance.

All payments will be sent in the form of direct deposit to a bank account. It may take up to several weeks to receive payment for study participation.

Your Social Security Number (SSN) will be needed to process your payment, as required by law. This information will be carefully protected. The Defense Finance and Accounting Service will report total payments of $600 or more within 12 months to the Internal Revenue Service (IRS).

WHAT HAPPENS IF I AM INJURED AS A RESULT OF TAKING PART IN THIS RESEARCH?

If at any time you believe you have suffered an injury or illness as a result of participating in this research, please contact the Principal Investigator (PI) of the study (Benjamin Ryan, benjamin.j.ryan14.mil@health.mil; 508-206-2408).

If you are injured because of your participation in this research and you are a DoD healthcare beneficiary (e.g., active duty military, dependent of active duty military, retiree), you are entitled to medical care for your injury within the DoD healthcare system, as long as you remain a DoD healthcare beneficiary.

If you are injured because of your participation in this research and you are not a DoD healthcare beneficiary, you are entitled to care for your injury at DoD hospitals or clinics, but care for your injury may be limited to a given time period, and your insurance may be billed. It cannot be determined in advance which DoD hospital or clinic will provide care. If you obtain care for research-related injuries outside of a DoD hospital or clinic, you or your insurance will be responsible for medical expenses.

For DoD healthcare beneficiaries and non-DoD healthcare beneficiaries: Transportation to and from hospitals or clinics will not be provided. No reimbursement is available if you incur medical expenses to treat research-related injuries. No compensation is available for research-related injuries. You are not waiving any legal rights. If you believe you have sustained a research-related injury, please contact the PI. If you have any questions, please contact the PI (Benjamin Ryan, benjamin.j.ryan14.mil@health.mil; 508-206-2408).

HOW WILL YOU PROTECT MY PRIVACY AND THE CONFIDENTIALITY OF RECORDS ABOUT ME?

To protect your privacy, all of your research-related records including data sheets will be labeled or "coded" with an assigned research participant number that will not include any identifiable information such as your name or social security number. Dr. Ryan will keep the link between your participant number and your name in a locked cabinet or password-protected computer on a restricted-access folder on our shared drive. The principal investigator and study coordinator are the only people who will be able to match your research participant number with any of your personal identifying information. The link between your name and participant number will be destroyed when the protocol is closed. All the study data that we get from you will be kept locked up or in password-protected computer files. Financial information, such as social security number and bank account number that is required for direct deposit of compensation for research, will be kept in a separate locked file cabinet from the research records. Only the principal investigator (or designee) will have access to this cabinet. These records will be destroyed upon project completion and compensation is complete.

When the results of the research are published or discussed in conferences, no information will be included that would reveal your identity to others. Specific permission to use photographs or video recordings of you and the manner in which they may be used will be requested and documented in an Audio/Visual Image Release form. If you do not sign the photo release form, no photos of you will be taken. If any photographs or video recordings are taken of you inadvertently, they will be destroyed immediately. You do not have to sign a photo release to participate in this study.

Authorized representatives of the following groups may need to review your research and/or medical records as part of their responsibilities to protect research participants:

- US Army Medical Research & Development Command Institutional Review Board responsible for review and oversight of human research
- DoD, FDA, and other Federal offices charged with regulatory oversight of human research
- US Army Research Institute of Environmental Medicine's Office of Medical Support and Oversight (OMSO)
- US Army Research Institute of Environmental Medicine's Office of Research Quality and Compliance

Once information that personally identifies you is removed from your data, then your data or blood specimens may be used for future research studies or given to other researchers for future research studies without additional permission from you. You will not benefit from the potential future use of data or specimens.

Complete confidentiality cannot be promised for military personnel, because information bearing on your health may be required to be reported to appropriate medical or command authorities.

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

WHAT IF I DECIDE NOT TO PARTICIPATE IN THIS RESEARCH?

It is your choice whether you want to participate in this research. You can choose not to be in the study now without any penalty or loss of benefits to which you are entitled.

If you decide to participate, you can stop taking part in this research at any time without any penalty or loss of benefits to which you are entitled. Deciding not to participate now or withdrawing at a later time does not harm, or in any way affect future relationships with USARIEM. You do not have to disclose the reason for withdrawal if you choose to do so.

You may withdraw by verbal, email, or telephone communication with the study PI (Benjamin Ryan, benjamin.j.ryan14.mil@health.mil; 508-206-2408)

If you do decide to withdraw, your compensation will be pro-rated based on the number of hours/blood samples collected you completed. Any data collected up until the point of withdrawal will be retained for future analysis and stored with all other study data.

WHAT COULD END MY PARTICIPATION IN THE RESEARCH?

The Principal Investigator may withdraw you from participating in this research if circumstances arise which warrant doing so such as if you are unwilling or unable to complete the study procedures or requirements. The Principal Investigator will make the decision and let you know if it is not possible for you to continue. Your taking part in the study may be stopped without your consent if it is determined by the Principal Investigator that remaining in the study might be dangerous or harmful to you.

WHAT IF ANY NEW INFORMATION IS FOUND OUT?

During the course of the research, the investigators will tell you of any new findings that might cause you to change your mind about continuing in the study. The PI and/or designee will inform you of any new information verbally and/or with a written document. If new information is provided to you, the investigators will obtain your consent to continue participating in this study.

WHO SHOULD I CALL IF I HAVE QUESTIONS OR CONCERNS ABOUT THIS RESEARCH?

If you have questions about the research at any time, you should contact the PI (Benjamin Ryan, benjamin.j.ryan14.mil@health.mil; 508-206-2408).

If you have questions regarding your rights as a research participant, you may contact the HQ USAMRDC IRB Office at 301-619-6240 or by email to usarmy.detrick.medcom-usamrmc.other.irb-office@health.mil. Alternatively, you can also contact the USARIEM Office of Research Quality and Compliance at 508-206-2371 or by email to usarmy.natick.medcom-usariem.mbx.usariem-rqc-protocol@health.mil.

By signing below, I agree that I have been provided time to read the information describing the research study in this consent form. The content and meaning of this information has been explained to me. I have been provided with the opportunity to ask questions. I voluntarily consent to participate in this study.

By signing this form, I have not given up any of my legal rights as a research participant.

SIGNATURE OF RESEARCH PARTICIPANT

Printed Name of Participant

Signature of Participant | Date

CONSENT DISCUSSION CONDUCTED BY:

Printed Name | Date Received