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PARTICIPANT CONSENT FORM

Title of Study: 'Central blood volume shifts in healthy adults with varying levels of fitness: Effects on lung diffusing capacity'

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Research/Study Coordinator:	**Desmond Young**	**Ph: 780-492-8027**

Why am I being asked to take part in this research study?

You are being asked to be in this research study that seeks to look at how changes in the volume of blood entering the heart impact lung blood vessel function. This study will not involve any medications for experimental purposes.

This form contains information about the study. Before you read it, a member of the study team will explain the study to you in detail. You are free to ask questions if there is anything you do not understand. You will be given a copy of this form for your records.

What is the reason for doing the study?

Evidence shows that fitness and biological sex affect how well oxygen moves from the lungs to the blood. Yet, the reasons for these differences are unknown. Differences might come from how well the body can respond to changes in how much blood enters the heart. This study aims to look at how lung blood vessels respond to changes in how much blood enters the heart. We are comparing the responses across fitness levels and between sexes. To change how much blood enters the heart, we will use positive and negative pressure around your legs (lower body positive pressure [LBPP], and lower body negative pressure [LBNP]). To do this, we will use a vacuum to pull blood away from the heart or to push blood toward the heart. We can also change the volume of blood entering the heart by tilting a bed while you are lying down. Tilting your head up pushes blood toward your legs, and tilting your head down pushes blood toward your head and lungs.

What will happen in the study?

This study consists of 5 visits, each of which are 1–2 hours (<10 hours total). For visits 1–4, we ask that you report to the laboratory after refraining from alcohol and heavy exercise for 12 hours, as well as from consuming food and caffeine for 4 hours prior to the laboratory visit. All visits will happen on separate days with at least 24 hours between visits. All visits will take place within 4 months.

Visit 1: Screening, lung and exercise tests (~2 hours).

On this visit, you will report to the Clinical Physiology Laboratory in the Clinical Sciences Building. To start, one of the study members will go through the informed consent form with you. You can ask any questions you may have. After getting your consent, we will ask questions about your health history. You will also fill out a form to make sure that the exercise part of the study is safe for you (PAR-Q+). The PAR-Q+ will tell you whether you need to seek further advice from your doctor or a qualified exercise professional before becoming more physically active. You will fill out a second form to tell us how much physical activity you do (PASB-Q). You will then complete lung function and exercise tests.

1. *Lung Function Test*: The lung function test involves a series of breathing maneuvers to measure how fast you can fill and empty your lungs, how much air your lungs can hold, and how well gas passes from your lungs into your bloodstream.
2. *Hemoglobin*: A drop of blood will be collected from your fingertip from a small prick. This drop of blood is used to measure hemoglobin, which is needed for calculating how well gas passes from your lungs into your bloodstream.
3. *Exercise test*: The exercise test measures your peak exercise capacity on a stationary bike. The test starts easy and gets harder in increments until maximal effort is reached. The test usually lasts about 15 minutes; the first ~70% of this test is easy. You will breathe through a mouthpiece, and we will monitor your heart rate, blood pressure, oxygen saturation, how hard you are working, and how much blood your heart is pumping. We will collect one more drop of blood to measure hemoglobin after exercise, as described in #2.

After this visit, we will look at your data to make sure you qualify for the study. No matter what, we will give you a copy of your lung function test and exercise test results. We will also explain your results and answer your questions.

Visit 2: Blood Volume Movement and Blood Vessel Function (~2 hours).

During this visit, a trained professional will insert a catheter into your forearm. The catheter will let us measure the pressure in your veins. You will then do several 6-second breath holds during lower body positive (LBPP) and negative pressure (LBNP), or during head up (HUT) and head down tilt (HDT). The breath holds let us look at your lung blood vessel function. This day will start with coaching and practice on how to perform these breath-holds. Each stage of LBNP/LBPP or HUT/HDT will have 2 breath-holds. We will measure your heart rate, blood pressure, vein pressure, and oxygen saturation throughout. We will collect a small blood sample (less than a teaspoon; 1 mL) from your catheter during each stage.

1. *IV line:* A small intravenous (IV) line will be inserted into a vein close to your elbow. We will use the IV for two reasons. First, we will collect a small (~6 mL) blood sample to measure the hemoglobin and the sex hormones in your blood. Second, we will measure the pressure in your vein. Vein pressure is measured like blood pressure in your arteries, except vein pressure is much lower so we cannot use an

arm cuff. Instead, we can measure your vein pressure by connecting your IV line to a sensor. Once the IV line is in place you will not feel the blood sample or the pressure measurements.

2. *LBNP/LBPP or HUT/HDT:* For LBNP/LBPP, you will lie down with your lower body inside a fiberglass box. A kayak skirt around your hip bone will seal your lower body inside the box. Your legs will have enough room to extend fully in the box. You will then undergo several stages where we change the pressure in the box. The LBPP/LBNP stages range between +40 mmHg and −80mmHg to simulate increases and decreases in the blood volume around the heart and the lungs. These pressures will be as stressful on the body as standing up (−80 mmHg) and laying with your feet above your head (+40 mmHg). A digital pressure monitor will measure the LBNP/LBPP pressures, and the desired pressures will be achieved using a vacuum pump (controlled by a trained member of the study team). For HUT/HDT, you will lie down on a "tilt" table while it is flat like a bed. You will then undergo several stages where we change the angle of the table. The tilt table will be adjusted electronically to the appropriate angle required for the stage. The HUT/HDT stages range between 90° (equivalent to standing up) and −12° (laying with your feet above your head). A member of the research team will tell you whether you will do LBNP/LBPP or HUT/HDT. You will only do one of the two.
3. *Breath-holds*: You will complete two breath-holds during each stage of LBNP/LBPP or HUT/HDT, including the reference stage at 0 mmHg or 0° tilt. The breath-hold maneuver will begin with you breathing normally through a mouthpiece. A researcher will cue you to empty your lungs as much as possible, then to take a full breath in and hold your breath for 6 seconds. After 6 seconds you will exhale through the mouthpiece. We will then remove the mouthpiece, and you will be able to breathe normally again.

Visit 3: Exercise and Blood Vessel Function (~2 hours).

During this visit you will do the same breath holds as visit 2. You will do the breath holds at rest and during easy to very hard exercise. We will measure your heart rate, blood pressure, and oxygen saturation throughout. We will also collect a fingertip prick blood sample during each exercise stage. Lastly, a trained professional will collect a blood sample from a vein in your forearm.

1. *Exercise*: You will exercise on the same stationary bike as you did your exercise test on Visit 1. You will bike at different intensities from 20% to 100% of the maximum intensity that you achieved on your exercise test. You will bike at each stage for about 2 minutes. During that time, you will do a breath-hold in the same way as described for Visit 2. We will repeat each stage twice. You will be able to take a break between exercise stages. You will complete no more than 5 different exercise stages.
2. *Blood sample:* We will collect a small (~5 mL) blood sample from a vein in your forearm to measure the sex hormones in your blood.

Visit 4: Ultrasound Imaging and Blood Volume (~2 hours).
During this visit, you will complete the same pressure or tilt challenge as visit 2 and the same exercise as visit 3. During all stages, a trained professional will take pictures of your heart by ultrasound. Next, a trained professional will insert an IV catheter into your forearm. You will then do a carbon monoxide rebreathe test so we can measure your blood volume.

1. *Carbon monoxide rebreathe:* A small volume of carbon monoxide will be mixed with 100% oxygen in a sealed bag. You will breathe in the contents of this bag, hold your breath for 10 seconds, and continue to rebreathe the same gas for two minutes. You will then lay still for eight minutes. We will take a blood sample (2 mL) from your IV before the rebreathe and a second sample (2 mL) eight minutes after the rebreathe test.

Visit 5: Computed Tomography (CT) Imaging (~1 hour).
The CT scan is a special type of X-ray that will be used to examine your lungs. You will be asked to lay on a table with just the upper part of your body inside the CT scanner. You will need to remain still and, at times, hold your breath for about 10–20 seconds during the test.

What are the risks and discomforts?
Participation in this study may involve some added risks or discomforts. Precautions and screenings will be in place to minimize these risks. These risks include:

Lung Function and Exercise Tests: There is risk associated with exercise, whether in our laboratory or in day-to-day life. Risks include temporary fatigue, shortness of breath, or muscle soreness. These discomforts usually stop within minutes of finishing exercise.

There is a very small risk of a serious cardiac event, such as an arrhythmia, heart attack or death, associated with heavy exercise in healthy people (less than 9 in 10,000). If you experience chest pain, lightheadedness, or clammy skin, we will stop the test for your safety. Lab personnel who are trained in CPR will supervise the exercise trials. If an abnormal response is detected, our lab has an adverse event protocol which will be implemented. If necessary, 911 will be called.

There are no foreseeable risks associated with breathing room-air or mixed gas mixtures. Some gas mixtures you breathe will contain trace amounts of carbon monoxide and helium gas. The small quantities of these gases will not harm you and will leave your body quickly. These gas mixtures are regularly used in clinical tests of lung function. You will not feel any symptoms from the trace amounts of carbon monoxide used in your lung function test.

Lower-body Negative Pressure and Head Up Tilt: There is a small risk of brief lightheadedness and fainting during lower-body negative pressure and head up tilt. However, we will monitor your blood pressure and heart rate and we will stop the test if we see your blood pressure drop. We also ask that you tell us if you feel light-headed,

sweaty, or have “tunnel” vision. If you feel any of these symptoms we will stop the test and you should feel better right away.

Finger Prick Blood Sample: You may feel minor discomfort as your finger is pricked.

Ultrasound Imaging: There are no known risks to ultrasound imaging of the heart or blood vessels. However, you may feel some discomfort during the heart imaging as the ultrasound probe will be pressed against your chest. If an abnormal finding is discovered, we will inform you of this and one of the study physicians will follow up with you regarding the results.

IV Lines and Blood Samples: A trained professional will insert your IV lines and perform your venous blood draw. The trained professional will stay in the room for the whole trial to make sure no problems arise. Risks of an IV line in your vein and venous blood draws include bruising, clot formation, or infection. These risks are rare (less than 1%) in participants who have the IV line in place for less than 5 hours. You may feel some discomfort when we insert the IV line. We will lower all the risks by having a trained professional perform the procedures under sterile conditions.

Risks related to IV lines include bleeding from the site and infection of the site. These risks are rare (less than 1%). To lower these risks, a trained professional will place the IV with good technique and sterile precautions. We will clean the skin site with an antiseptic, and we will use sterile, commercially available IV lines. We will use full sterile precautions for blood sampling from your IV as well. Our blood sampling uses a closed system, which is the same as what is often used in hospitals.

We will attach your IV to a venous pressure transducer. Once we attach the lines there are no further risks or discomforts with measuring your venous pressure.

Carbon Monoxide Rebreathe: The carbon monoxide rebreathe includes breathing more carbon monoxide than you would be exposed to in day-to-day life. In large doses carbon monoxide can be toxic because it competes with oxygen in the blood and could cause you to get too little oxygen around your body. Because of this risk, we have several safety strategies in place. First, you will get a known dose of carbon monoxide that has been shown to be safe in past research. The dose you will get will cause ~6% carbon monoxide saturation in your blood and you should not feel any symptoms from this dose. The dose will increase your carbon monoxide saturation like a regular smoker. Other research has shown that up to ~20% carbon monoxide saturation is not harmful. We will measure your carbon monoxide saturation using a finger clamp. We will stop the protocol if your carbon monoxide saturation goes above 12%. We will also stop the protocol if you or the research team see any symptoms of carbon monoxide poisoning. Symptoms to look out for include headache, nausea, or cognitive impairment. We also have 100% oxygen available. Breathing pure oxygen will make sure your body gets enough oxygen. It will also speed up carbon monoxide removal from your blood. Because you are getting all the carbon monoxide at once, any symptoms should happen during the protocol and get better with time.

Quantitative CT Imaging of the Lungs: The CT scan includes exposure to radiation from X-rays. This radiation exposure is for research purposes only and is in addition to any radiation needed for your medical care. X-rays can damage cells, but at low doses, the body is usually able to repair these cells. Radiation risk is believed to be related to the total lifetime exposure. The risk from radiation exposure in this research study is very low.

The CT scan that you are having as part of this research study is not the same as a clinical exam. It is designed to answer specific research questions. The exam will be reviewed by a medically qualified person and read to an appropriate standard. Research studies are not a replacement for clinical studies and are often less comprehensive. Although the imaging you will have in this study is being undertaken for research purposes only, it is possible that doctors may notice something that could be important to your health. If so, we will contact you to explain what was observed. If required, we will refer you to an appropriate clinic for follow-up. It will be your choice whether to proceed with additional tests and/or treatments to evaluate what we observed.

Pregnancy: The CT scan may not be safe during pregnancy. If you are pregnant or breastfeeding, you will not be able to take part in the study. If you are a woman of childbearing potential not using contraception, you must have a negative urine pregnancy test before starting the study. We will provide a test for you. Acceptable contraception includes tubal ligation, oral contraceptive, barrier methods (intrauterine device, diaphragm, female condom, male condom). Abstinence is an acceptable form of contraception. But, if you practice abstinence you must use another method of birth control if you become sexually active during the study.

Blood Pressure: There are no risks associated with the use of finger or arm cuffs to examine blood pressure. Some individuals may feel discomfort and numbness in the fingertip during long testing sessions. This goes away immediately upon cuff removal.

Other Risks: There are no risks associated with recording heart rate or oxygen saturation.

What are the benefits to me?
There will be no direct benefit to you from participating in this study. This study will generate knowledge of the mechanisms by which aerobic fitness and biological sex impact the blood vessels in the lungs.

What happens if I am injured because of this research?
In the case of research-related side effects or injury, medical care will be provided by referring you for the appropriate medical care.

What are the rights of participants in a research study?
You will be told, in a timely manner, about new information that may be relevant to your willingness to stay in this study. Your rights to privacy are legally protected by federal and provincial laws that require safeguards to ensure that your privacy is respected.

By signing this form you do not give up any of your legal rights against the study doctor, sponsor or involved institutions for compensation, nor does this form relieve the study doctor, sponsor or their agents of their legal and professional responsibilities.

Do I have to take part in the study?
Being in this study is your choice. If you decide to be in the study, you can change your mind and stop being in the study at any time, and it will in no way affect the care or treatment that you are entitled to.

Withdrawal of consent
You can stop being in the study at any time, and this will not affect the care you are entitled to receive. If you decide you wish to stop, the study team will go over your options with you and will document your decision in the study record. You do not need to sign anything to stop being in the study.

What will it cost me to participate?
Participating in this study will not cost you anything. You will be reimbursed for parking or transit costs associated with study visits.

Will I be paid to be in the research?
You will not be paid for participating in this study. However, you will be reimbursed for parking or transit expenses, at the rate of $15.00 per visit up to 5 visits. As a thank you for your time and effort, you will receive $50 after completing the study. You will get the full $50 no matter how much of the study you do.

Privacy and Confidentiality
During this study we will be collecting information (or "study data") about you. We will use the data to help answer research questions and we will share (or "disclose") your information with others such as other researchers.

Below we describe in more detail how your data will be collected, stored, used and disclosed.

What data will we be collecting?
During this study we will be collecting data about you. Examples of the types of data we may collect include your name, your ethnic background, your date of birth, your age, your health history and your medications. We will only look for and collect the information that we need to do the research. We will get this information by asking you questions and doing the tests outlined in this form.

How will the study data be stored?
The study data we collect which will include your name will be securely stored during and after the study. At the University of Alberta, regulations say we have to keep the study data stored for at least 5 years after the end of the study.

The study staff will not release your name to anyone unless required by law.

How will the study data be used?
Your study data will be coded (with a number) so that it no longer contains your name or anything else that could identify you. Only investigators will be able to link your coded study data to you. The risk to your privacy, then, should be very small.

When the study is done, the investigators may place your coded study data into a secure database. The coded data may then be used to answer other research questions in the future. Only researchers who have the training and experience to do the research (also known as "qualified researchers") will be allowed to use the data and in no way can your data be linked back to you.

Who will be able to look at my data?
During research studies, the data we get must be accurate. Therefore, your study data may also be looked at by people from: the University of Alberta auditors and members of the Research Ethics Board.

By signing this consent form, you are saying it is ok for the principal investigator/staff to collect, use and disclose information from your study data as described above.

If you would like to see the study data collected about you, please ask a member of the research team. You will be able to look at the study data about you and you can ask for any mistakes to be corrected. We will have to wait until your participation in the study is complete to share your study data with you.

If you leave the study, we will not collect new information about you, but we will need to keep the data that we have already collected.

What if I have questions?
If you have any questions about the research now or later, or if you experience any adverse effects, or think that you have suffered a research related injury please contact **Desmond Young (780-492-8027) or Michael Stickland (780-492-3995).**

If you have any questions regarding your rights as a research participant, you may contact the University of Alberta Research Ethics Office at ethics@ualberta.ca. This office is independent of the study investigators.

The study investigators do not have any conflicts of interest to disclose. This study is funded by a federal grant called the NSERC Discovery Grant. This means that the Institution and researchers are getting money from the granting agency/funder to cover the costs of doing this study. This funding does not involve any personal payments to the research team.

How do I indicate my agreement to be in this study?

By signing below, you understand:

- That you have read the above information and have had anything that you do not understand explained to you to your satisfaction
- That you will be taking part in a research study
- That you may freely leave the research study at any time
- That you do not waive your legal rights by being in the study
- That the legal and professional obligations of the investigators and involved institutions are not changed by your taking part in this study.

SIGNATURE OF STUDY PARTICIPANT

_____
Signature of Participant

_____ _____
Name of Participant Date

SIGNATURE OF PERSON OBTAINING CONSENT

_____
Signature of Person Obtaining Consent

_____ _____
Name of Person Obtaining Consent Date