UNIVERSITY OF CALGARY
CONSENT TO PARTICIPATE IN RESEARCH

TITLE: Investigating Functional Optical Coherence Tomography and Hypercapnia to Diagnose and Treat Neurogenic Orthostatic Hypotension

SPONSOR: Libin Cardiovascular Institute

Study Investigators: Dr. Jacquie Baker PhD (Post-Doctoral Fellow), Dr. Satish Raj MD (Principal Investigator), Dr. Richard Wilson (Co-Principal Investigator), Dr. Robert S Sheldon MD (Co-Investigator) & Dr. Carlos Morillo (Co-Investigator)

Introduction

Dr. Raj and associates from the Libin Cardiovascular Institute of Alberta at the University of Calgary are leading a research study. This consent form is only part of the process of informed consent. It should give you the basic idea of what the research will involve. If you would like more details, please ask. Take the time to read this carefully and to understand this. You will receive a copy of this form. You are being asked to be in this study because you are over 18 years old and are either a patient with Neurogenic Orthostatic Hypotension (NOH) or a healthy person. Your participation in this study is voluntary.

WHY IS THIS STUDY BEING DONE?

The Autonomic (or "automatic") Nervous System (ANS) controls important functions, including heart rate and blood pressure (BP). When someone stands, and gravity tries to pull blood away from the brain, the ANS works to maintain BP and brain blood flow. Neurogenic Orthostatic Hypotension (NOH) occurs when our "fight-or-flight" part ("sympathetic") of the ANS fails. When the sympathetic part fails, BP can drop a lot when standing (≥20/10 mmHg). When this happens blood flow and oxygen delivery to the brain is reduced and this can cause lightheadedness, nausea, and fainting.

The brain needs blood flow and oxygen to function, and an inability to control these variables may greatly impact brain health. A solution to improve BP when standing, is to increase sympathetic activity by breathing higher levels of carbon dioxide (hypercapnia). In healthy volunteers, small increases in the amount of inhaled carbon dioxide has increased BP in the standing position and improved symptoms.

Also, it is important to know what is happening to sympathetic activity and brain blood flow. Recently, we found a new way to measure sympathetic activity using optical coherence tomography (OCT). OCT is used in eye clinics around the world to take pictures of the eye. We found that we can also use OCT to look at blood vessels at the back of the eye to help measure sympathetic activity and brain blood flow.

The aims of the current study are to use carbon dioxide and take pictures of the eye using OCT in patients with NOH and healthy volunteers to:

(a) Explore the effects of breathing carbon dioxide on BP and brain blood flow
(b) Explore OCT as a new tool to measure sympathetic activity and brain blood flow
(c) Determine if a device that increases CO_2 while standing will work as a new therapy

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

40 patients diagnosed with NOH and 40 age-matched healthy controls will take part in this study

WHAT WILL HAPPEN IF I TAKE PART IN THIS STUDY?

The study will require you to withhold alcohol, caffeine and moderate- to heavy-intensity exercise for 12 hours prior to the study. We will also ask that you have your last large meal 2 hours prior to the study. You can drink water as needed. When you arrive to the lab, a team member will describe the study to you, answer any questions and a written informed consent form will be acquired if you choose to participate.

A research team member will ask you questions about current medications you are on and other disorders you may have. We will also review the inclusion/exclusion criteria for the study. All study equipment will be shown to you at which point we will begin to prepare for the study.

You will sit in a chair where you will be able to lean forward and look into the OCT machine. A series of practice scans will be done in order for you to become comfortable with the procedure. These scans take 1.5 seconds and do NOT involve any air-puff or drugs. Once you are comfortable with the OCT procedure, you will begin the study with a 10-minute baseline in the seated position, where we will measure how much CO_2 you breathe out ($ETCO_2$) over the last 5 minutes. We will also record blood pressure, heart rate, brain blood flow, and breathing patterns using the following equipment:

- Finger and arm blood pressure cuffs
- 3 skin electrodes to measure heart rate
- A Transcranial Doppler (TCD) which will use a band around your head, with an ultrasound-like probe at either your left or right temple
  - You will be fitted with a facemask. The facemask will be connected to a tube supplied with gas from a programmable gas mixing system (RespirAct™). The RespirAct™ is an investigational use device distributed by Thornhill Research Inc. (Toronto, Ontario, Canada)
- OCT scans will be taken at defined intervals during each intervention

You will complete up to 5 Active Stand Tests (AST) lasting 5 minutes each. You will remain seated for a minimum of 5 minutes before each AST. You will be asked to do 5 different breathing tasks while you stand. Breathing tasks will start 1 minute before you stand (while sitting down) and will last until the end of each AST.

The 5 Active Stand Tests consist of:

a) Normal breathing (not coached) without $ETCO_2$ clamped
b) Normal breathing (not coached) with $ETCO_2$ levels maintained at baseline level
c) Normal breathing (not coached) with $ETCO_2$ levels 5mmHg above your normal level
d) Normal breathing (not coached) with $ETCO_2$ levels 10mmHg above your normal level
e) Normal breathing (not coached) with $ETCO_2$ levels 10mmHg above your normal level and ETO_2 levels at 50mmHg

B-D will be done in a random order. A will always be done first to determine your normal $ETCO_2$. E will be performed last. All tests will be separated by a minimum of 5 minutes of resting normal breathing. OCT scans will be taken while you are sitting and standing during each test.

HOW LONG WILL I BE IN THIS STUDY?

The total time of study should be ~2.5 hours.

ARE THERE ANY POTENTIAL RISKS OR DISCOMFORTS THAT I CAN EXPECT FROM THIS STUDY?

***Blood Pressure Cuff*:** You may find it uncomfortable to have an inflated cuff placed around the finger and the arm for an extended period of time.

***Electrodes*:** Sticky patches will be placed on your chest and limbs to record your heart rate and may be uncomfortable or occasionally cause a rash.

Active Stand Test: There might be light-headedness, headache, nausea or feelings of faintness during the active stand test. These symptoms usually resolve rapidly upon returning to the seated position.

Transcranial Doppler (TCD): Ultrasound gel will be applied which may cause a rash. The Doppler probe will be in direct contact with the head, which may be uncomfortable. The headband will be snug, but there will be opportunities to loosen it off during the recovery periods, and the headband is adjustable.

Function Optical Coherence Tomography (fOCT): OCT does NOT emit any radiation or harmful rays or substances. It is a normal piece of equipment in eye clinics. OCT uses a bright light to look at the eye, which does not injury the eye.

RespirAct: You will be fitted with a facemask connected to a tube supplied with gas from a programmable gas mixing system. The mask or breathing tasks might be uncomfortable.

Breathing Protocols: During the breathing protocols, you might experience light-headedness, dizziness, headache or nausea, which usually resolve rapidly upon returning to breathing room air. Breathing low amounts of oxygen is similar to high altitude. During this exercise, you may experience increased breathing and heart rate. Some participants have described the sensation of a mild headache; however, this diminishes quickly upon breathing normal air. Between breathing exercises you will breathe normal air for a minimum of 5 minutes. If you experience discomfort and would like to pause or end the study, a study member will do so.

Tape allergy reaction: Tape will be applied to fix the mask to your face, which may cause a rash, or discomfort when removed

COVID-19: This study involves in-person interactions with research staff, and will require increased time within a health care facility. If you require public transportation, this may increase contact with other people. To reduce your risk, all research staff will follow standard Alberta Heath Services protocol. Throughout the study protocol, all research staff will wear proper personal protective equipment including gloves, masks face shields and/or goggles. Proper hand sanitization protocols will also be used throughout.

ARE THERE ANY POTENTIAL BENEFITS IF I PARTICIPATE?

If you agree to be in this study, there will not be a direct benefit to you. The results of this study will help us understand the effects of CO_2 in patients with NOH to improve blood pressure and symptoms when standing. We also hope that this study will lead to the development of new tool, which may benefit millions with diseases similar to yours.

WHAT OTHER CHOICES DO I HAVE IF I CHOOSE NOT TO PARTICIPATE?

Your participation in this study will be entirely voluntary. As a patient we encourage you to talk to your doctor about your choices before you decide if you will take part in this study. You may decide not to take part in this study. Non-participation in this study will not adversely affect your relationship with the involved researchers or other University of Calgary staff.

CAN I STOP BEING IN THE STUDY?

Yes. You can decide to stop at any time. Tell the study doctor if you are thinking about stopping or decide to stop. They will tell you how to stop safely.

CAN THE RESEARCHERS REMOVE ME FROM THIS STUDY?

The researchers may end your participation in this study if your safety and welfare are at risk, if you do not follow instructions or if you miss scheduled visits. The researchers or the study sponsor might also decide to stop the study at any time.

WHAT IF RESEARCHERS DISCOVER SOMETHING ABOUT ME?

During the study, the researchers could learn something about you they didn't expect. For example, the researchers may find out that you have another medical condition. The researchers will consult with medical experts to evaluate the findings and will then share these results with you. You will be helped with arranging appropriate follow-up care.

I consent for the researchers to share findings with me:

❑ YES
❑ NO

WITHDRAWAL OF STUDY DATA

You may withdraw from the study and cancel this consent at any time without any impact on your current and future health care. If you decide to stop being in the study, or are removed from the study, the data collected about you up to that point will remain part of the study. However, you may request to withdraw your data if the data hasn't been analyzed and we will not use your data in our research. Once data analysis has begun, your data cannot be withdrawn.

WILL I BE PAID FOR PARTICIPATING, OR DO I HAVE TO PAY FOR ANYTHING?

You will not be paid for your participation in this research study. We will cover parking costs on the study day at the University of Calgary - Foothills Hospital Campus in the TRW Parking Lot.

WILL INFORMATION ABOUT ME AND MY PARTICIPATION BE KEPT CONFIDENTIAL?

The researchers will do their best to make sure your private information is kept confidential, unless required by law. Information about you will be handled as confidentially as possible, but there is always the potential for an unintended breach of privacy. The research team will handle data according to the Data Management Plan as outlined below:

- All identifiable information about you will be replaced with a code. A master list linking the code and your identifiable information will be kept separate from the research data.
- All research data and records will be maintained in a secure location at the University of Calgary. Only authorized individuals will have access to it.

- We hope to publish the results of this study as a scientific paper to help other doctors treat their patients. Your privacy will be protected and you will never be identified by name or by a description of you.

HOW LONG WILL INFORMATION FROM THE STUDY BE KEPT?
The researchers intend to keep the research data and records for at least **5** years. Any future use of this research data is required to undergo review by a Research Ethics Board.

ACCESS TO MEDICAL RECORDS (PATIENTS ONLY**)**
If you have been diagnosed with NOH, we will need to access your medical records
My medical records may be accessed.

❑ YES

UNIVERSITY OF CALGARY REQUIREMENTS FOR IN-PERSON ACTIVITIES:
In order to be in-person on a University of Calgary campus, students, faculty, staff and visitors to campus, including research participants, are required to show proof of full vaccinations status against COVID-19.

USE OF DATA FOR FUTURE RESEARCH
My research data may be kept for use in future research to learn about, prevent or treat other health-related problems.

❑ YES
❑ NO

CONTACT FOR FUTURE RESEARCH
University of Calgary researchers may contact me in to ask me to take part in other research studies.

❑ YES
❑ NO

IF I SUFFER A RESEARCH-RELATED INJURY, WILL I BE COMPENSATED?
It is important that you tell the researchers if you believe that you have been injured because of taking part in this study. In the event that you suffer injury as a result of participating in this research, no compensation will be provided to you by the University of Calgary, Alberta Health Services or the Researchers. However, you still have all your legal rights. Nothing said in this consent form alters your right to seek damages.

HOW CAN I FIND OUT ABOUT THE STUDY RESULTS?
Individual study results will be made available to the participants on request.

SIGNATURES

Your signature on this form indicates that you have understood to your satisfaction the information regarding your participation in the research project and agree to participate as a participant. In no way does this waive your legal rights nor release the investigators or involved institutions from their legal and professional responsibilities. If you have further questions concerning matters related to this research, please contact:
Dr. Jacquie Baker (403) 210-3819, Dr. Satish R Raj (403) 210-6152 or Dr. Richard Wilson (403) 220-8460

If you have any questions concerning your rights as a possible participant in this research, please contact the Chair, Conjoint Health Research Ethics Board, University of Calgary at 403-220-7990.

Participant's Name	Signature and Date
Investigator/Delegate's Name	Signature and Date
Witness' Name	Signature and Date

The University of Calgary Conjoint Health Research Ethics Board has approved this research study.
A signed copy of this consent form has been given to you to keep for your records and reference.