Is blood flow through IPAVA and PFO related to breath-hold and SCUBA diving-induced pulmonary hypertension?

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UNIVERSITY OF OREGON
RESEARCH SUBJECT INFORMATION AND CONSENT FORM

TITLE OF THE RESEARCH STUDY: Is blood flow through IPAVA and PFO related to breath-hold and SCUBA diving-induced pulmonary hypertension?

STUDY INVESTIGATOR: Andrew T. Lovering Ph.D. and Colleagues

FUNDING: This study is funded by the Fulbright US Scholar Program and Burroughs Welcome Fund

KEY INFORMATION SUMMARY

1. This is a research project and participation is voluntary
2. Summary of the research:
    - Purpose of the study: To determine the effects of a patent foramen ovale (PFO) on pulmonary pressure pre and post SCUBA diving. We are also interested to know if a pulmonary vasodilator has a measurable impact on pulmonary pressure pre and post SCUBA diving.
    - Duration: the anticipated duration is 7.5 hrs over 2 days.
    - List of procedures:
        1. Measure lung function with various breathing tests
        2. Measure heart function and lung blood pressure using ultrasound and
        3. Measure blood pressure with a blood pressure cuff
        4. Measure blood markers of inflammation from various IV blood draws
        5. Measure blood flow through your PFO and blood vessels in your lungs called shunts using a technique called saline contrast echocardiography
        6. You will take a placebo on one day and sildenafil on another day
        7. You will perform two SCUBA dives up to 30 meters and last up to 75 minutes, one dive on each study day.
        8. You will ingest a telemetric pill prior to your dives to measure your core body temperature pre- and post-dive.
3. Reasonable, foreseeable risks or discomforts:
    - There are risks of breathlessness, dizziness and light headedness for lung function measures but no risks associated with ultrasound measures of pulmonary pressure
    - There are no risks associated with measuring heart function and blood pressure
    - There are risks of pain, bleeding, bruising and infection for intravenous blood draws
    - There are risks of temporary dizziness and confusion with saline contrast echocardiography,
    - There risks of dizziness, low blood pressure and visual disturbances with ingestion of sildenafil
    - There are risks of decompression sickness, arterial gas embolism and oxygen narcosis/toxicity with SCUBA diving
4. Reasonable, expected benefits: There are no direct benefits for subjects, only generalizable knowledge to be gained.
5. Alternative procedures or course of treatment, if any: There are no available alternative procedures or courses of treatment for this study

You are being recruited for participation in this study because you have significant experience SCUBA diving. If you qualify and decide to participate, then you will be one of the 50 individuals we plan to study.

This study meets the definition of a clinical trial. 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 the results. You can search this Web site at any time.

WHAT WILL HAPPEN?
Prior to **all study visits**, you will be reminded via telephone or e-mail to refrain from consuming caffeine or medications for 12 hours prior to the study, and to not exercise or consume alcohol for 24 hours prior to the study. You will also be asked to not eat for 2 hours prior to the study.

Male subjects may go shirtless or wear a loose-fitting scrub top for all visits involving echocardiographic imaging. Female subjects will need to wear a sports bra and a loose fitting scrub top for all visits involving echocardiographic imaging. This allows the upper body to be covered but also allows for imaging of the heart and the placement of small electrodes that record your heart rate.

DETAILED VISIT INFORMATION:

Visit #1 Screening, Enrollment and First SCUBA dive:
This visit will take approximately 4.5 hours. Upon arrival to the University of Split Medical School, a researcher will provide an overview of the study and informed consent.

You will be excluded if:

1) You disclose a previous history of coronary artery disease (ischemic heart disease such as angina, heart attack, myocardial infarction).
2) You are currently taking medications or herbal supplements for any heart or respiratory disease that you cannot stop taking for 48 hours prior to testing (seasonal allergy medication or contraceptives not included in exclusion medications).
3) You have any previous history of any condition that would prevent you from performing SCUBA diving.
4) You are someone who is pregnant or trying to become pregnant.
5) You are taking Sildenafil or products (PDE-5 inhibitors) similar to Sildenafil, such as Tadalafil (Cialis) and Vardenafil (Levitra/Staxyn). If you can refrain from using PDE-5 inhibitors for 48 hours before each study day then you will be allowed to participate.
6) You are taking NITRATES and other Nitric Oxide donors.
7) Volunteers with history of obstructive diseases of the gastrointestinal tract including diverticulosis, diverticulitis, inflammatory bowel disease, peptic ulcer disease, Crohn's disease, ulcerative colitis, or previous GI surgery will not use a telemetric pill.

Anyone with child bearing potential will be required to take a urinary pregnancy test before all visits. The pregnancy test will be self-administered in a restroom facility but will be read by the Investigators. If it is discovered that a subject is pregnant, they will be excluded from the study and encouraged to see their physician.

Echocardiographic Screening: For the echocardiogram (ultrasound of the heart) a small probe will be placed against your ribcage. This probe sends and receives ultrasound waves to make an echocardiogram image. This procedure is very similar to an ultrasound that is taken to image a baby inside of its mother. For the screening, an intravenous (IV) catheter will be placed in your forearm and will be used to inject saline contrast. Saline contrast is made by mixing sterile salt water with a small amount of air to make a solution of

saline with very tiny bubbles called microbubbles. This solution will be injected into the IV while an echocardiogram image is obtained. The microbubbles will travel to your heart where they are very easy to see with the echocardiogram. You will also be asked to breathe 100% oxygen for 5-10 minutes while we repeat the screening procedures (about1.25 hrs).

Blood draw: We will take about 2 tablespoons of your blood (21 mL) using the IV catheter that was placed in your forearm and used to inject saline contrast. We will measure markers of inflammation in your blood.

Lung Function Screening: You will perform non-invasive lung function tests by breathing through a mouthpiece that is connected to a computer (about 15 minutes).

If the above tests determine that you meet our criteria to be included in the study, you will be allowed to proceed with the study.

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Initials of Participant
By initialing above you understand that the results of these tests at Visit #1 will determine your eligibility to continue with the study.

Only subjects with a history of obstructive diseases of the gastrointestinal tract including diverticulosis, diverticulitis, inflammatory bowel disease, peptic ulcer disease, Crohn's disease, ulcerative colitis, or previous GI surgery will not use a telemetric pill.

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Initials of Participant

By initialing above you are consenting to take the telemetric pill and you do not meeting the exclusion criteria above for telemetric pill use.

Heart and lung measures before and after SCUBA diving. You will be instrumented with a forehead oxygen sensor, heart rate monitor and blood pressure cuff. We will make measures of your heart and lung blood pressure using ultrasound before SCUBA diving (about 30 min).

Prior to starting your dive, you will ingest a telemetric pill to measure your core body temperature pre-and post-dive. If you do not swallow the telemetric pill 5-10 hours prior to your dive, you will be asked to insert the telemetric pill as a suppository.

You will perform a SCUBA dive to depths up to 30 meters and lasting up to 75 minutes with decompression profiles determined using V-planner software according to the varying permeability model (about 1.25 hrs). The Dive Master will ensure that all divers have a ‘dive buddy’, a SCUBA-certified individual of similar or greater experience than you have. You are encouraged to identify a ‘dive buddy’ to accompany you, but in the event that you are unable to secure a ‘dive buddy’, the Dive Master will ensure that you have a ‘dive buddy’ for your dive.

You will ingest a placebo or sildenafil (50 mg oral) upon resurfacing and coming aboard dry land. You will not know which intervention you are receiving. The order in which you take the interventions (placebo or sildenafil) will be randomized. Whichever intervention you are randomly assigned to on your first visit, you

will be assigned the other on your second visit. During the hour wait until peak effect, you will be instrumented with forehead saturation, heart rate monitor and a blood pressure cuff. Pulmonary artery pressure, cardiac output and right and left heart function will be measured using ultrasound approximately 1 hour after placebo or sildenafil administration. In addition, you will have another small blood draw taken (about 2 tablespoons or 21 mL) after your dive, approximately 1 hour after ingestion of the placebo or sildenafil (about 1.5 hrs).

Visit #2: Second SCUBA dive:
This visit will take approximately 3 hours.

Heart and lung measures & blood draw before and after SCUBA diving. You will be instrumented with a forehead oxygen sensor, heart rate monitor and blood pressure cuff. We will make measures of your heart and lung blood pressure using ultrasound before SCUBA diving. We will also take a small blood sample (about 2 tablespoons or 21 mL) before your dive (about 30 min). Prior to starting your dive, you will ingest a telemetric pill to measure your core body temperature pre-and post-dive. If you do not swallow the telemetric pill 5-10 hours prior to your dive, you will be asked to insert the telemetric pill as a suppository.

You will perform a SCUBA dive to depths up to 30 meters and lasting up to 75 minutes with decompression profiles determined using V-planner software according to the varying permeability model (about 1.25 hrs). The Dive Master will ensure that all divers have a 'dive buddy', a SCUBA-certified individual of similar or greater experience than you have. You are encouraged to identify a 'dive buddy' to accompany you, but in the event that you are unable to secure a 'dive buddy', the Dive Master will ensure that you have a 'dive buddy' for your dive.

You will ingest a placebo or sildenafil (50 mg oral) upon resurfacing and coming aboard dry land. If you were randomly assigned to the sildenafil on your first visit, you will receive the placebo on this visit, and vice versa. You will not know which intervention you receive. During the hour wait until peak effect, you will be instrumented with forehead saturation, heart rate monitor and a blood pressure cuff. Pulmonary artery pressure, cardiac output and right and left heart function will be measured using ultrasound approximately 1 hour after placebo or sildenafil administration. In addition, you will have another small blood draw taken (about 2 tablespoons or 21 mL) after your dive, approximately 1 hour after ingestion of the placebo or sildenafil (about 1.5 hrs).

WHAT ARE THE RISKS?

Risks associated with the lung function testing and plethysmography includes cough, shortness of breath, light-headedness, dizziness, and possible temporary loss of consciousness. Lung function testing performed in our lab is a routine assessment performed in pulmonary function labs all over the world according to American Thoracic Society and European Respiratory Society standards. You can stop the test at any time if you feel any of the above symptoms. The probability and severity of these risks is very low.

Risks associated with placement of the intravenous catheter (IV) include pain and/or bleeding during placement, vasovagal syncope, hematoma (pooling of blood under the skin), infection, and vessel blockage. The placement of the IV may cause some discomfort with rare bleeding or bruising at the puncture site. It also carries the risk of infection. Some individuals may also feel like fainting at the site of needles or blood (vasovagal response). A total of 21 mL (about 2 tablespoons) of blood will be drawn through an IV. We use aseptic techniques and sterile needles and IV catheters, so the probability of experiencing any severe side effects such as infection is low and not different from the risks of an IV being placed for the purpose of

drawing blood for a routine clinical test. To mitigate these potential risks, you will be continually monitored Andrew Lovering PhD (IV placement) and colleagues. In addition, you will be safely and comfortably positioned on either a gurney or IV chair. In this way, the potential risks outlined above (e.g., vasovagal response) is mitigated.

The saline-bubble injection at rest or during exercise carries a remote risk of temporary dizziness, confusion, difficulty breathing, and an extremely remote risk of brain injury or stroke. Air is not typically injected into the vein because of the risk of an air blockage (which includes the risk of heart attack or stroke). Mixed saline (saltwater), either alone or with 5% sugar in water has been used to help see the ultrasound pictures (echocardiogram) for over thirty years. Saline contrast bubble injections are routinely used to screen for the presence of a patent foramen ovale in the clinic. The American Society of Echocardiography Guidelines (2014) state that "…life threatening reactions are rare (<1 in 10,000)" when using contrast injections (including bubbles with protein shells) and The European Association of Echocardiography (2009) has stated that "… the evidence shows that contrast echocardiography is very safe in clinical practice." This includes using stabilized bubbles with protein shells and we only use non-stabilized saline contrast bubbles in our lab. We only use a small amount of air mixed with saline, thus the probability of any severe adverse reaction is very low.

Specific precautions with the administration of Sildenafil are generally restricted to potential interactions with other medications and the potential to cause low blood pressure. Adverse reactions to Sildenafil are most commonly dizziness, low blood pressure, visual disturbances and the potential for an erection lasting longer than 4 hours in males. This is considered a serious condition that requires medical intervention. Biological half-life of Sildenafil is 4 hours. Aside from the possibility of acute decrease in blood pressure associated with Sildenafil, there may be other unknown risks.

Male subjects will be asked to go shirtless for all echocardiography and exercise studies. Accordingly, subjects could potentially feel embarrassed or have modesty issues by being shirtless. To minimize the risk of embarrassment or modesty issues, subjects will be allowed to wear a loose fitting scrub top (provided by the researchers) that allows for concealment of upper body but also allows for echocardiographic imaging and EKG electrode placement. Female subjects will not go shirtless, but will wear a scrub top during the entire study. The probability of this risk is low and severity of these risks is low.

Risk for subjects undergoing SCUBA diving are similar to those you experience with recreational diving. You will dive twice to the depths of up to 30m, where you will stay for up to 75 minutes, so that during the resurfacing your decompression stops will be determined using standardized diving protocols and recreational dive tables as determined by a diving computer, Galileo, Uwatec. The dives will be done in the presence of a safety diver, a paramedics doctor, while the doctors working at the Institute for hyperbaric medicine will be thoroughly informed about the diving protocol and schedule. During the dive, the following risks are possible: 1) decompression sickness – a condition in which air bubbles dissolved in tissues suddenly become released into bloodstream due to the decrease of the ambient pressure. Common symptoms include pain in the joints, extremities, dizziness, nausea, vomiting, extreme tiredness, paralysis, collapse and fainting. The incidence of decompression sickness among divers is generally low, ranging from 0.013% to 1.25%. Decompression sickness is primarily related to the depth and duration of the dive, as well as to the duration of decompression while resurfacing. 2) Arterial gas embolization – the bubbles can reach arterial system in people with defects in the interatrial wall of the heart; 3) Embolization – during the quick decompression, bubbles of oxygen can move from tissues into circulation; 4) Expansion lung injury and pneumonmediastinum – can happen during the breath hold while resurfacing; 5) Gas/Oxygen narcosis – a result of toxic effects of high oxygen pressure on nerve conducting, symptoms comparable to drunkenness

may happen; 6) Oxygen toxicity – toxic effects of oxygen can be caused by the high quantity of absorbed oxygen, and can present as burning sensations in the lungs, spasms, dizziness and vomiting. Because you are an experienced diver, the probability of these risks is very low, although the severity is moderate.
The Dive Master will ensure that all divers have a 'dive buddy', a SCUBA-certified individual of similar or greater experience than you have. You are encouraged to identify a 'dive buddy' to accompany you, but in the event that you are unable to secure a 'dive buddy', the Dive Master will ensure that you have a 'dive buddy' for your dive. The risks of using the temperature pills include mechanical injury to the mucus membranes if adequate care is not used. Risks of the temperature pill will be minimized by explaining the procedures to the volunteers. Additionally, ample lubricant (suppository) or water (oral) will be provided to the volunteer. Volunteers with history of obstructive diseases of the gastrointestinal tract including diverticulosis, diverticulitis, inflammatory bowel disease, peptic ulcer disease, Crohn's disease, ulcerative colitis, or previous GI surgery will not use a telemetric pill.

To minimize risks, the Principal Investigator and co-investigators are CPR and first aid trained. During all exercise and recovery procedures you will be non-invasively and continuously monitored for vital signs using: 1) electrodes to monitor electrical activity of your heart (called ECG), 2) a forehead probe to monitor oxygen saturation in your blood and your heart rate and 3) blood pressure.

An automated electronic defibrillator (AED) with a spare AED battery and spare AED pads, bottled oxygen and face mask and a standard first aid kit are available at the laboratory of Dr. Zeljko Dujic in the department of integrative physiology at the University of Split School of Medicine in Split, Croatia, where testing site where all testing and screening will be performed.

According to American Heart Association's guidelines, in the event of an adverse cardiopulmonary event, we will begin CPR, call 911 (211 in Croatia), and will begin CPR as required until emergency medical personnel arrive.

WILL I BE COMPENSATED FOR THIS STUDY?

<u>Subject Compensation (maximum of $50 USD, about 330 HRK paid via cash at the end of the study)</u>:

Visit #1: $30.00 USD: Completing the informed consent and echocardiographic screening and blood draw will pay 5.00 USD. The pulmonary function tests will pay $5.00 USD. Subjects who choose not to participate upon review of the informed consent or are excluded based on any findings during this visit will be paid for their degree of visit completion that is $5.00 USD. If the subject decides not to participate after reviewing the informed consent; $10.00 USD for participation in the screening procedures; total compensation for reviewing the informed consent and participating in screening is $10.00 USD. Subjects will be paid $20.00 USD for performing the SCUBA dive and post-dive measures. Compensation will be converted to the local currency based on the US dollar amount. It will be converted from US dollars to Croatian Khuna.

Visit #2: $20.00 USD: Subjects will be paid $20.00 USD for SCUBA diving and participating in the post dive measures.

Any subject that withdraws (or is withdrawn) before the end of the study will receive prorated payment up to the point of completion.

Can I withdraw from participation? If you choose to terminate your participation prior to the end of the study, your compensation will be adjusted to the protocols completed. You may withdraw from participation

at any time without affecting your standing with the University of Oregon and the Department of Human Physiology of The University of Split Medical School. If you withdraw from the study, any de-identified data collected up to that point will remain part of the study database and will not be removed.

Are there benefits to the study? This study will not make your health better. This study is only being done to gather information. This study will help to further understand how blood flows through the lungs in healthy human subjects. Understanding blood flow through the lungs in healthy humans may help to determine the best ways to treat persons with lung disease or complications such as pulmonary hypertension (high blood pressure in the lung) and acute respiratory distress syndrome (RDS).

You may choose not to take part in this study **at any time** before completing the entire study. If you choose to stop participating before the end of the study you **will not be penalized**. You will be paid for the visits you complete before dropping out. A physician will not review the results. The technician is not authorized to make a diagnosis, but if any abnormal indications are noted during the study procedures, you will be encouraged to see your physician.

Who can answer my questions? You may speak with Dr. Andrew Lovering at any time about any questions you have about this study. You may contact Dr. Lovering by calling 1+541-346-0831 or e-mail at lovering@uoregon.edu. If you have questions regarding your rights as a research subject, you can contact the Research Compliance Services, 5237 University of Oregon, Eugene, OR 97403, 1+541-346-2510 in the event you have questions about your rights as a research subject. You may speak to Dr. Zeljko Dujic at any time about any questions you have about this study. You may contact Dr. Dujic by calling +385 91 5268 114 or e-mail at zeljko.dujic@mefst.hr. In order to contact the United States from Croatia, +011 will need to be inserted before the actual number.

What are my rights if I choose to take part in this study? Taking part in this research study is your decision. You do not have to take part in this study, but if you do, you can stop at any time. Your decision whether or not to participate will not affect your relationship with the University of Oregon, the Department of Human Physiology, the Cardiopulmonary Laboratory or with the University of Split Medical School. Participation or non-participation as a subject in any study will not affect your academic standing. You do not waive any liability rights for personal injury by signing this form. All forms of medical diagnosis and treatment whether routine or experimental, involve some risk of injury. In spite of all precautions, you might develop medical complications from participating in this study. If such complications arise, the researchers will assist you in obtaining appropriate medical treatment. The investigators may stop you from taking part in this study at any time if it is in your best interest, if you do not follow the study rules, or if the study is stopped. If you are physically injured because of the project, you and your insurance company will have to pay your doctor bills. If you have no insurance, the cost of treatment will be your responsibility. If you experience harm because of the project, you can ask the State of Oregon to pay you. A law called the Oregon Tort Claims Act limits the amount of money you can receive from the State of Oregon if you are harmed. If you have been harmed, there are two University representatives you need to contact. Here are their addresses and phone numbers:

General Counsel
Office of the President
University of Oregon
Eugene, OR 97403
(541) 346-3082

Research Compliance Services
University of Oregon
Eugene, OR 97403
(541)-346-2510

There is a local ethics committee located in Split, Croatia, and they can be reached at:

dr. sc. Lana Barać
Kontakt:
e-mail: uzz@mefst.hr
tel.: 021 557 929

What about confidentiality? Any information that is obtained in connection with this study and that can be identified with you will be de-identified using a random number coding system to protect you. With the exception of potentially sharing de-identified data with other investigators for research purposes, your de-identified data will remain confidential and will be disclosed only with your permission. De-identified data can be shared with other investigators without obtaining additional informed consent.

Each subject folder will be stored in a locking file cabinet inside the primary investigators locking office located at the Split Medical School until Dr. Lovering travels back to the United States. Subsequently, all hard copy data will be scanned into electronic format while in Croatia and saved on a password protected and fingerprint protected locked hard drive and hand carried by Dr. Lovering back to the United States. All hard copies will be left with collaborator Dr. Zeljko Dujic, who will store these hard copies indefinitely. These electronic format data will subsequently stored inside the primary investigators locking office located at the University of Oregon Cardiopulmonary and Respiratory Physiology Lab.

Research Compliance Services and/or authorized representatives of the Food and Drug Administration (FDA), and other various public and federal entities may need to review records of individual subjects. As a result, they may see your name in the decoder sheets, but they are bound by rules of confidentiality not to reveal your identity to others. The list of names, codes and decoding information will be kept after the study results have been published for at least 7 years, according to National Institutes for Health guidelines. Non-published data will be kept at least 10 years after collection. Your signature indicates that you have read and understand the information provided above, that refusal to participate will involve no penalty or loss of benefits to which you are otherwise entitled, that you willingly agree to voluntarily participate, that you may withdraw your consent at any time and discontinue participation without penalty or loss of benefits to which you are otherwise entitled, that you will receive a copy of this form, and that you are not waiving any legal claims, rights, or remedies.

We are not collecting any data with respect to racial or ethnic origin, political opinions, religious or philosophical beliefs, trade union membership, processing of genetic data; biometric data for the purposes of unique identification, health data; and/or sex life or sexual orientation information. We are not using automated processing of data for decision making about the individual, including profiling.

De-identified data may potentially be shared with other investigators for research purposes related to this study and unrelated to this study.

Note: Compensation from participation in Human Subjects Research studies is taxable income. If your compensation totals $600 or more in a calendar year, the University is required to report the income to the IRS. The University requires its departments to track participant compensation and may contact you to complete a Form W-9 for tax reporting purposes. Because of the federal and University tracking

requirements, your name will be associated with participation in research. Department and University administrators will have access to this information, but will not have access to research data.

I have had an opportunity to have my questions answered. I have been given a copy of this form. I agree to take part in this study.

Date	Signature of Participant	Print Name
Date	Signature of Individual Obtaining Consent	Print Name