Sildenafil for Prevention of Swimming-Induced Pulmonary Edema (SIPE)

Duke IRB #: Pro00100971

NCT #: NCT03686813

DUKE UNIVERSITY HEALTH SYSTEM

Consent to Participate in a Research Study
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Concise Summary

The purpose of this study is to determine whether the drug sildenafil prevents or reduces the likelihood of developing pulmonary edema (fluid in the lungs) during swimming or diving (immersion pulmonary edema or swimming-induced pulmonary edema, SIPE). The information we learn by doing this study may help us to recommend preventive measures for individuals who experience this condition.

If you participate in this study you will undergo a COVID test, exercise testing, a breathing test, ultrasound of your lungs and possibly your heart, and have a small sample of blood taken. You will then drink Pedialyte™ (an oral electrolyte solution) then perform exercise head-out in cold (20°C) water for 40 minutes. During the exercise you will be monitored for symptoms of SIPE. If you develop SIPE you will be removed from the water and if needed receive treatment. This exercise will be performed twice, with the exercise periods at least one week apart. In addition to the Pedialyte, you will receive either sildenafil or an inactive tablet. Neither you nor the investigators will know which one you received until the study is over. If you develop symptoms a chest x-ray may be needed.

If you are interested in learning more about this study, please continue to read below.

You are being asked to take part in this research study because you have experienced immersion pulmonary edema (swimming-induced pulmonary edema, SIPE). Research studies are voluntary and include only people who choose to take part. Please read this consent form carefully and take your time making your decision. As your study doctor or study staff discusses this consent form with you, please ask him or her to explain any words or information that you do not clearly understand. We encourage you to talk with your family and friends before you decide to take part in this research study. The nature of the study, risks, inconveniences, discomforts, and other important information about the study are listed below.

Please tell the study doctor or study staff if you are taking part in another research study.

Dr. Richard Moon will conduct the study and it is funded by the US Navy. The sponsor of this study, the Navy, will pay Duke University to perform this research, and these funds may reimburse part of Dr. Moon's salary.

WHO WILL BE MY DOCTOR ON THIS STUDY?
If you decide to participate, Dr. Moon will be your doctor for the study and will be in contact with your regular health care provider throughout the time that you are in the study and afterwards, if needed.

WHY IS THIS STUDY BEING DONE?
The purpose of this study is to determine the effectiveness of the drug sildenafil in preventing SIPE in individuals who have experienced SIPE previously.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?
Approximately 40 people will take part in this study at Duke University Medical Center, with the goal of 20 subjects participating and completing testing.

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WHAT IS INVOLVED IN THE STUDY?
If you agree to be in this study, you will be asked to sign and date this consent form. You will have the following tests and procedures to make sure that you are eligible:

- Physical exam and medical history
- Vital signs
- Blood tests
- Electrocardiogram (EKG), a tracing of the electrical activity of the heart
- Breathing test (pulmonary function test, PFT)
- If you have not already had one, an echocardiogram and stress echo study
- Ultrasound scan of your lungs
- COVID testing

If you are eligible, following a 2 liter drink of Pedialyte (a flavored oral resuscitation fluid), you will exercise for 40 minutes on a bicycle in an immersion tank while breathing through a mask. An immersion tank is like a pool where your body is underwater and your head is out. The water is cold 19-21°C (66-70°F). The mask will measure how much oxygen your body consumes while you exercise. You will perform this exercise twice: once after taking a 50 mg tablet of sildenafil, and once after a dummy pill (placebo, an inactive substance in a form that looks like the active drug, sildenafil). Following the exercise study you will have another breathing test and ultrasound scans of your lungs.

The two exercise studies will be on different days at least a week apart. The order in which you take the drug and placebo (active drug then placebo or placebo then active drug) will be randomized (like drawing numbers from a hat) and the identity of the active drug and the placebo will be masked so that neither you nor the investigators will know which pill is taken for either day until the end of the study. During the exercise your heart and blood oxygen will be continuously monitored, and blood pressure will be measured every few minutes. You will also be monitored for manifestations suggesting SIPE development such as shortness of breath, cough or reduced blood oxygen level. If it is suspected that you may have SIPE you will be removed from the water, taken to a warm room and if needed, treated with oxygen and an inhaled medication (albuterol) that facilitates removal of water from your lungs. You may also undergo x-ray of your chest.

THERE ARE SEVERAL IMPORTANT CONSIDERATIONS:
- Participation in this study is voluntary.
- You may terminate your participation at any time.
- A blood sample will be obtained, from which DNA will be extracted and stored for possible future studies to determine whether there is a genetic predisposition to SIPE. You may decline this portion even if you participate in the exercise study. Your genes are made up of DNA. DNA is short for deoxyribonucleic acid. DNA contains information that determines in part the traits, such as eye color, height, or disease risk, that are passed on from parent to child.

HOW LONG WILL I BE IN THIS STUDY?
The study will last at least 7 days, however you may return home after the first study and come back to Duke for the second exercise study at a mutually convenient time. You can choose to stop participating at any time.

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Clinically relevant results of this research will be communicated with you as soon as they are known. When the study has been completed and the data fully analyzed the results will be communicated to you in writing.

WHAT ARE THE RISKS OF THE STUDY?
As a result of your participation in this study, you are at risk for the following side effects. You should discuss these with the study doctor and your regular health care provider if you choose. Sildenafil may cause some, all or none of the side-effects listed below.

Risks associated with sildenafil: With sildenafil administration, the common adverse reactions include headache, flushing, dyspepsia (upset stomach), nasal congestion, urinary tract infection, diarrhea, dizziness, nosebleeds, insomnia, and rash. These effects are generally mild to moderate, transient, and more common at the maximum recommended dose (100mg) and exposures above that. There is risk of visual disturbances, with alteration in color vision and excessive brightness, but these are also dose-dependent and reversible. Sudden vision loss in one eye has been reported rarely after with the use of sildenafil and other similar drugs. This effect is much less likely with only a single administration of sildenafil, and it is not possible to determine if these events are related to these drugs or to other factors.

More likely

- Headache
- Flushing
- Upset stomach
- Nasal congestion
- Nausea

Less likely

- Visual symptoms such as redness, pain or sensitivity
- A rapid heart rate or changes in your blood pressure.
- Abnormal vision
- Back pain, muscle pain
- Ringing in the ears or dizziness.
- Rashes.

If you develop SIPE it may be recommended that you receive albuterol by inhalation to facilitate clearance of the excess water from your lungs. Albuterol is a very safe drug with uncommon side effects, which can include the following: tremors, dizziness, nervousness, headache, insomnia, nausea, dyspepsia, nasal congestion, throat pain, increased heart rate, high blood pressure, bronchospasm, cough, bronchitis, wheezing.

Drug interactions: For your safety, you must tell the study doctor or nurse about all the prescription drugs, herbal products, over-the-counter (OTC) drugs, vitamins, and natural remedies that you are taking before you start the study and before taking any of these products while you are on the study.

In addition, during the exercise study you may become cold, or may develop SIPE, with accompanying shortness of breath, cough and low levels of blood oxygen.

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FOR THOSE OF REPRODUCTIVE POTENTIAL

Female

Being a part of this study while pregnant may expose the unborn child to significant risks, some of which may be currently unforeseeable. Therefore, pregnant women will be excluded from the study. If you are a woman of childbearing potential, a blood pregnancy test will be done (using 1 teaspoon of blood drawn from a vein by needle-stick), and it must be negative before you can continue in this study. If sexually active, you must agree to use appropriate contraceptive measures for the duration of the study. Medically acceptable contraceptives include: (1) surgical sterilization (such as a tubal ligation or hysterectomy), (2) approved hormonal contraceptives (such as birth control pills, patches, implants or injections), (3) barrier methods (such as a condom or diaphragm) used with a spermicide, or (4) an intrauterine device (IUD). Contraceptive measures such as Plan B (TM), sold for emergency use after unprotected sex, are not acceptable methods for routine use. If you do become pregnant during this study or if you have unprotected sex, you must inform your study physician immediately.

Male

Your participation in this research may damage your sperm, which could cause harm to a child that you may father while on this study. Such harm may be currently unforeseeable. If you are sexually active, you must agree to use a medically acceptable form of birth control in order to be in this study. Medically acceptable contraceptives include: (1) surgical sterilization (such as a vasectomy), or (2) a condom used with a spermicide. Contraceptive measures such as Plan B (TM), sold for emergency use after unprotected sex, are not acceptable methods for routine use. You should inform your partner of the potential for harm to an unborn child. She should know that if pregnancy occurs, you will need to report it to the study doctor, and she should promptly notify her doctor.

RISKS OF RADIATION:

If you take part in this research, you will have one or more medical imaging studies or treatments. The tests or treatments you will have include a chest x-ray. These tests or treatments involve a small amount of radiation. The radiation exposure from this research is about 200 microsievert. To give you an idea about how much radiation you will get, we will compare it to the amounts that people encounter in daily life. There is radiation that naturally occurs from space and from rocks in the soil. This natural radiation is greater at higher altitudes. This research gives you about the same amount of radiation as you would get from living in a high altitude city such as Denver for 12 days, or taking 4 airplane flights from New York to Los Angeles. The radiation dose we have discussed is what you will receive from this study only, and does not include any exposure you may have received or will receive from other tests.

A possible health problem seen with radiation exposure is the development of cancer later in life. This extra cancer risk is higher at younger ages and for girls and women. The extra lifetime risk of dying of a fatal cancer due to the radiation exposure from this research is minimal. At such low radiation exposures, scientists disagree about the amount of risk. These estimates are very uncertain, and there may be no extra risk at all.

Risks of Drawing Blood:

Risks associated with drawing blood from your arm include momentary discomfort and/or bruising. Infection, excess bleeding, clotting, or fainting are also possible, although unlikely.

Drug and Food Interactions:

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For your safety, you must tell the study doctor or nurse about all the prescribed medical foods and drugs, herbal products, over-the-counter (OTC) drugs, vitamins, natural remedies, and alcohol that you are taking before you start the study and before starting to take any of these products while you are on the study.

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?
If you agree to take part in this study, there may be direct medical benefit to you. You will learn whether sildenafil may reduce the possibility of future SIPE episodes. This information will be provided to you. We hope that in the future the information learned from this study will benefit other people who are susceptible to SIPE.

WILL MY INFORMATION BE KEPT CONFIDENTIAL?
Participation in research involves some loss of privacy. We will do our best to make sure that information about you is kept confidential, but we cannot guarantee total confidentiality. Your personal information may be viewed by individuals involved in this research and may be seen by people including those collaborating, funding, and regulating the study. We will share only the minimum necessary information in order to conduct the research. Your personal information may also be given out if required by law.

As part of the study, results of your study-related laboratory tests, x-rays, and procedures may be reported to the Navy. In addition, your records may be reviewed in order to meet federal or state regulations. Reviewers may include representatives and affiliates of the US Navy, the Duke University Health System Institutional Review Board, and others as appropriate. If any of these groups review your research record, they may also need to review your entire medical record.

All of the blood, urine and x-ray studies are being done only because you are in this study. The study results will be provided to you and/or sent to your physician at your request.

Expiration date or event for the retention of records
The study results will be retained in your research record for at least six years after the study is completed. At that time either the research information not already in your medical record may be destroyed or information identifying you may be removed from such study results at DUHS. Any research information in your medical record will be kept indefinitely. Some information collected in research studies is maintained in your medical record. However, for this study that information will be inaccessible until the end of the study, unless your physicians decide that it is necessary for your care.

This information may be further disclosed by the sponsor of this study. If disclosed by the sponsor, the information is no longer covered by federal privacy regulations. If this information is disclosed to outside reviewers for audit purposes, it may be further disclosed by them and may not be covered by federal privacy regulations.

While the information and data resulting from this study may be presented at scientific meetings or published in a scientific journal, your name or other personal information will not be revealed.

Some people or groups who receive your health information might not have to follow the same privacy rules. Once your information is shared outside of DUHS, we cannot guarantee that it will remain private. If you decide to share private information with anyone not involved in the study, the federal law designed to protect your health information privacy may no longer apply to the information you have shared. Other laws may or may not protect sharing of private health information.

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A representative from the sponsor may be present as an observer at certain study visits/procedures.

WHAT ARE THE COSTS TO YOU?

There will be no cost to you for the tests performed for the procedure or the experiment itself. You will also receive any treatment of the mild SIPE expected in this study at no cost. You or your insurance provider will be responsible and billed for any other costs of medical care, including copayments and deductibles. Routine medical care services are those that you would have received for your condition if you were not participating in this research study. Not all services are covered by insurance. Some procedures or scans may require pre-authorization by your insurance plan. We will notify you if we learn that a service is not covered by your insurance plan as part of the pre-authorization process. If it is not covered, you will be responsible for paying for it. The amount of your out-of-pocket expense will depend on your insurance plan. For beneficiaries with Medicare Advantage Plans, traditional Medicare is billed for the routine cost of a research study. You may have more or higher co-pays than with a Medicare Advantage plan. Please discuss the costs of the study with Dr. Moon. At your request, a Financial Counselor in the clinic may provide you with an estimate of costs for routine services.

The study sponsor, US Navy, has agreed to pay for services and procedures that are done solely for research purposes. Please talk with the study team about the specific services and procedures that the sponsor will pay for, and the ones for which you or your insurance will be responsible.

We will monitor your DUHS patient care charges to make sure that costs are directed appropriately. If you have any questions or concerns about appropriate billing, contact your study team coordinator so that he/she can help find a resolution.

WHAT ABOUT COMPENSATION?

You will be reimbursed up to $2000 for your expenses related to your participation (travel, lodging, food) for each single part of the experiment ($4000 for two exercise periods). In addition, $1000 will be paid to you for your participation in a complete study (two sessions at least a week apart). If you are withdrawn from the study or withdraw voluntarily, you will receive $100 for traveling to Duke for screening, and $450 for each exercise period. Payment received as compensation for participation in research is considered taxable income to the research subject. If payment to an individual exceeds $600 in any one calendar year, Duke University is required to report this information to the Internal Revenue Service (IRS). Research subject payments to a non-employee of Duke University exceeding $600 during any calendar year will result in a 1099 (Miscellaneous Income) form being issued to the individual and a copy sent to the IRS.

WHAT ABOUT RESEARCH RELATED INJURIES?

Immediate necessary medical care is available at Duke University Medical Center in the event that you are injured as a result of your participation in this research study. However, there is no commitment by Duke University, Duke University Health System, Inc., or your Duke physicians to provide monetary compensation or free medical care to you in the event of a study-related injury.

For questions about the study or research-related injury, contact Dr. Moon at 919-684-8762 during regular business hours and at 919-684-8111, pager ID #970-5290 after hours and on weekends and holidays.

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WHAT ABOUT MY RIGHTS TO DECLINE PARTICIPATION OR WITHDRAW FROM THE STUDY?
You may choose not to be in the study, or, if you agree to be in the study, you may withdraw from the study at any time. If you withdraw from the study, no new data about you will be collected for study purposes unless the data concern an adverse event (a bad effect) related to the study. If such an adverse event occurs, we may need to review your entire medical record. All data that have already been collected for study purposes, and any new information about an adverse event related to the study, will be sent to the study sponsor.

Your decision not to participate or to withdraw from the study will not involve any penalty or loss of benefits to which you are entitled, and will not affect your access to health care at Duke. Nonparticipation or withdrawal from this study will not affect your job status if you are a Duke employee and will not affect your grades if you are a Duke student. If you do decide to withdraw, we ask that you contact Dr. Moon in writing and let him know that you are withdrawing from the study. His mailing address is: Dept. of Anesthesiology, Box 3094, Duke University Medical Center, Durham, NC 27710, USA.

We will tell you about new information that may affect your health, welfare, or willingness to stay in this study.

The sponsor or regulatory agencies may stop this study at any time without your consent. Reasons why this might occur include large numbers of side effects of the study. If this occurs, you will be notified.

Photographs are taken to demonstrate protocols used in research studies. You will be asked if you agree to be photographed before any are taken. If taken, such photographs might be presented at meetings describing the research, in which case a bar will be placed in the photograph over the area of your eyes to make the photograph less identifiable. You will not be identified nor will your individual results discussed in such cases.

Please read the sentence below and put your subject initial next to your choice. No matter what you decide to do, your decision will not affect your care.

1. "I agree to be photographed."
_____
Subject's Initials

2. "I do not agree to be photographed."
_____
Subject's Initials

A description of this clinical trial will be available on https://clinicaltrials.gov/ as required by US 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.

WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?
For questions about the study or a research-related injury, or if you have problems, concerns, questions or suggestions about the research, contact Dr. Moon at 919-919-684-8762 during regular business hours and at 919-684-8111, pager ID #970-5290 after hours and on weekends and holidays.

For questions about your rights as a research participant, or to discuss problems, concerns or suggestions related to the research, or to obtain information or offer input about the research, contact the Duke University Health System Institutional Review Board (IRB) Office at (919) 668-5111.

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STATEMENT OF CONSENT

"The purpose of this study, procedures to be followed, risks and benefits have been explained to me. I have been allowed to ask questions, and my questions have been answered to my satisfaction. I have been told whom to contact if I have questions, to discuss problems, concerns, or suggestions related to the research, or to obtain information or offer input about the research. I have read this consent form and agree to be in this study, with the understanding that I may withdraw at any time. I have been told that I will be given a signed and dated copy of this consent form."

_____	_____ _____
Signature of Subject	Date Time
_____	_____ _____
Signature of Person Obtaining Consent	Date Time