Study Title

Phase I/II Randomized Cross-over Study of Hypertonic Saline on Airway Inflammatory Response to Inhaled Wood Smoke

NCT number NCT03851406
Document Date 05/25/2023

University of North Carolina at Chapel Hill
Consent to Participate in a Research Study
Adult Participants

Consent Form Version Date: May 25, 2023
IRB Study # 18-1895
Title of Study: Phase I/II Randomized Cross-over Study of Hypertonic Saline on Airway Inflammatory Response to Inhaled Wood Smoke
Principal Investigator: Terry Noah, MD
Principal Investigator Department: Pediatrics
Principal Investigator Phone number: (919) 962-5136
Principal Investigator Email Address: terry_noah@med.unc.edu
Funding Source and/or Sponsor: Department of Defense (DOD)

Study Contact Telephone Number: (919) 843-6598
Study Contact Email: chris_brooks@med.unc.edu

What are some general things you should know about research studies?
You are being asked to take part in a research study. To join the study is voluntary.
You may choose not to participate, or you may withdraw your consent to be in the study, for any reason, without penalty.

Research studies are designed to obtain new knowledge. This new information may help people in the future. You may not receive any direct benefit from being in the research study. There also may be risks to being in research studies. Deciding not to be in the study or leaving the study before it is done will not affect your relationship with the researcher, your health care provider, or the University of North Carolina-Chapel Hill. If you are a patient with an illness, you do not have to be in the research study in order to receive health care.

Details about this study are discussed below. It is important that you understand this information so that you can make an informed choice about being in this research study.

You will be given a copy of this consent form. You should ask the researchers named above, or staff members who may assist them, any questions you have about this study at any time.

What is the purpose of this study?
Deployment of military personnel has been associated with increased respiratory illness likely due, in part, to inhalation of unusual particulate matter (PM), such as from burn pits. Inflammation is a key initial response to inhaled particulates. Our center has developed a protocol using inhaled wood smoke particles (WSP) as a way to study PM-induced airway inflammation. Exposure to wood smoke particles causes symptoms, even in healthy people, such as eye irritation, cough, shortness of breath, and increased mucous production. The purpose of

this research study is to see if a single treatment of inhaled hypertonic saline (HS) can diminish this PM-induced airway inflammation by rapidly clearing the WSP inhaled particles from airway surfaces. The exposure will be 500 ug/m^3 of WSP for 2 hours, with intermittent exercise on a bicycle and rest. The wood is burned in a typical wood stove and piped into the chamber.

You are being asked to be in the study because of your participation in the "Smoke Screen" study, IRB 15-1775.

Are there any reasons you should not be in this study?

You should not be in this study if you have asthma or other chronic health problems, if you are a smoker, or if you are pregnant, trying to get pregnant, or breastfeeding an infant. You also should not participate in this study if you have orthopedic problems which prevent you from riding a bicycle.

How many people will take part in this study?

There will be approximately 14 people in this research study.

How long will your part in this study last?

Before you participate in this study, you should have completed our general screening protocol, IRB #98-0799, and our woodsmoke screening protocol, IRB #15-1775. There are 10 visits for this study, and it should take up to 6 months to complete all of these visits. Period 1 of the study involves a baseline visit, which should be at least 2 weeks after you complete the woodsmoke screening protocol, and a training visit. You will return the very next day after your training visit for a 30 minute follow up scan. The next visit is the exposure visit, which will last 8 hours and must be within 12 weeks of the baseline visit. You will return for a follow up visit 24 hours after the exposure. A study coordinator will call you within 3 – 7 days after your exposure to ask you how you are feeling. There will be a 2-week washout from the exposure and you will return for a second baseline visit to begin period 2 of the study. You will return the very next day for a 30 minute follow up scan. Within 12 weeks of your second baseline visit, you will return for your second exposure and the 24 hour follow up. We will ask you to return within 5-10 days for checkout visit, which lasts about 30 minutes.

If you have an illness or event during your enrollment in the study, we will wait to continue your participation until you are healthy. If you test positive for Covid, we will wait at least 90 days. If this causes your visits to be out of window, the Principal Investigator may want you to return for safety labs and lung function to ensure we can continue with the study safely.

Visit 0 Baseline: 2 hours

Visit 1 Training Day: 4.5 hours

Visit 2: 0.5 hours

Visit 3 (Period 1) and Visit 7 (Period 2) WSP exposure: 8 hours

Visit 4 (Period 1) and Visit 8 (Period 2) 24hrs post WSP exposure: 1 hour

Visit 5 Baseline (Period 2): 4 hours

Visit 6: 0.5 hours

Visit 9 Study Completion: 0.5 hours

What will happen if you take part in the study?

Your first visit you will arrive to the lab for the baseline **Visit 0.** This will be at least 2 weeks after you complete smoke screen study, and you must avoid vitamins A, C, E and multivitamins, as well as any non-steroidal anti-inflammatory medications for 4 days before each visit. You will be given an opportunity to read the consent form, and the study will be explained to you. We will answer all of your questions. We will then collect your **medical history**, including any **medications** that you take. If you are female, you will have a *urine pregnancy test*, and it must be negative. We will check your **vital signs**, including your temperature, your heart rate, your respiratory rate and the oxygen concentration in your blood. We will listen to your chest to be sure you aren't wheezing. One of the study doctors will do a **physical exam**. We will do an **EKG** – we will place patches on your chest, your arms and legs to collect a ready of the electrical activity of your heart. You will do a **lung function** test for us, you will take a full breath in and blow it out as hard and as fast as you can. You must be vaccinated for Covid 19 according to current public health recommendations.

You will then return for your **Visit 1** or training visit. If this is more than 7 days from Visit 0 and if you are a female, then you will have another urine pregnancy test. When you have the exposure, you will be exercising on a bicycle. We will show you the bike at this visit and how it works, and we will measure your breathing to be sure you are exercising enough for the study. This is measured by minute ventilation, which will be based on your body surface area. We will place an EKG monitor on you to watch your heart rate and rhythm during the exercise. We'll show you how to place the finger probe, so we can monitor your oxygen, and how to connect the blood pressure cuff. We will monitor your blood pressure intermittently during the exposure.

After riding the bicycle for 15 minutes, you will undergo a measurement of your lungs' silhouette. This is called a lung transmission scan, and a baseline evaluation of muco-ciliary clearance (**MCC**) – the MCC scan measures how quickly mucus is cleared from your airways. Two small, radioactive discs (Americium 241) will be taped to your upper and lower back to determine your position in front of the gamma camera. The Americium 241 discs are the same sources found in household smoke detectors and will expose you to a very tiny radiation dose (which is included in the total dose of radiation you are exposed to in the study). You will then be seated in front of a gamma camera, which is a device for measuring radioactivity. After measuring background radioactivity for 15 minutes, we will place a plate that contains a small amount of Cobalt 57 (a radioactive material) in front of your chest to create a picture of the shape of your lungs, similar to a weak chest X-ray. For the MCC scan, you will inhale radiolabeled

particles and sit in front of the gamma camera to track the movement of the particles out of your lungs for 2 hours. You will have intermittent rest breaks during this period.

Then you will have a **sputum induction**. For this test, you will inhale a heavy mist made from salt water, at a concentration that is higher than the concentration of salt normally found in your body. This loosens secretions in your lungs, and allows you to cough the sample into a cup. We will monitor your lung function between levels of salt water, and you will inhale 3 different levels, starting at 3%, then 4% and finally 5%.

You will return the very next day for your **Visit 2**, which will be a brief follow up lung scan. This completes the MCC scan.

It will be important for you to follow all public health recommendations for Covid -19 during the time you are participating in this study, including wearing a mask, limiting potential exposure and maintaining physical distancing from people who you don't live with or who are not vaccinated.

Your next visit will be your **Visit 3** exposure day. This visit must be within a 6 weeks from your visit 0. This will be your first wood smoke exposure for the study. You will be randomly assigned to one of two groups; subjects in one group will inhale salt water at a 5% level at the start of the MCC scan during the first treatment period (this visit) and no inhaled salt water for the second treatment period. The second treatment period is visit 7, the second wood smoke exposure visit. Subjects in the other group will receive the same treatments but in the opposite order. The order in which you receive inhaled 5% salt water is determined completely by chance, as if by the toss of a coin. At this visit the following assessments and procedures will be performed:

- Vital signs, oxygen saturation, review any changes in your health or medications since the last visit.
- Symptom questionnaire
- Urine Pregnancy Test (if not previously performed within 7 days)
- Blood draw - We will draw about 20cc of **blood** from you, including blood to go to Labcorp to measure your complete blood count, and to look for markers of inflammation. We will also look to see if you have a gene, which can determine how you respond to air pollution. The rest will be used for labs just for the research.
- Exhaled breath condensate (**EBC**) - Breath condensate collection is a method for obtaining components in exhaled breath that are indicators of inflammation. This method is useful for human studies due to the noninvasive nature of the procedure. You will be asked to breathe normally, in through your nose, and out through your mouth, into a section of tubing for 10 minutes.
- Lung function testing
- You will enter the exposure chamber. You will start on the bicycle, exercising for 15 minutes, and then rest for 15 minutes. We will measure your breathing for the last few minutes of each exercise session. You will be in the chamber for 2 hours total, and near the end we will ask you to complete the symptom questionnaire again.
- Symptom questionnaire (immediately prior to exit from the chamber)

- Immediately following exit from chamber, subjects will do a lung transmission scan and the MCC will be started.
- At the start of the MCC scan, you will either inhale the 5% salt water or no treatment – depending on what treatment group you are in.
- Symptom questionnaire following completion of the 5% salt water (if received)
- Complete MCC

Six hours after you entered the woods smoke chamber, the following assessments and procedures will be performed:

- Symptom questionnaire
- EBC
- Lung function testing
- Sputum Induction
- Blood draw

We will check your vital signs before you are discharged, and we will send you home with contact information for a study doctor in case you have any concerns about your health related to the study.

You will return the next day for a follow up visit, or **Visit 4.** We will:

- Review any adverse events
- Vital signs, oxygen saturation
- Symptom questionnaire
- A 30 minute follow up lung scan.
- EBC
- Lung function testing
- Blood draw – we will draw about 20cc of blood
- Sputum induction

You will be contacted by phone 3-7 days following Visit 4 to assess for any delayed adverse events.

At least two weeks after you have completed visit 4, you will return for your **Visit 5**, which is your baseline visit for period 2. The following procedures will occur:

- Review medical history and adverse events
- Urine pregnancy test
- Vital signs, oxygen saturation
- MCC
- Lung function testing
- Blood draw – we will draw about 4cc of blood
- Sputum Induction

You will return the very next day for your **Visit 6**, which will be a brief follow up lung scan. Within twelve weeks of Visit 5, you will have your **Visit 7,** this will be your second wood smoke

exposure visit. This will be just like Visit 3 except you will receive the opposite treatment. So if you inhaled 5% salt water on Visit 3, then you will receive no treatment on Visit 7. Then, 24 hours after visit 7, you will return for your **Visit 8**, which is just like Visit 4.

No phone call will be made after Visit 8 since you will be returning for a study completion visit as below.

You will come back to the research lab 5-10 days after you finish the exposure session for **Visit 9,** for a check out visit.

- Review any adverse events
- Vital signs, oxygen saturation
- If you have any health symptoms or concerns, a study doctor will do a physical examination.

What are the possible benefits from being in this study?

Research is designed to benefit society by gaining new knowledge. You will not benefit personally from being in this research study.

What are the possible risks or discomforts involved from being in this study?

Wood smoke: Breathing wood smoke in this study might cause coughing, wheezing, shortness of breath, irritation of the eyes, ears, nose, throat or lungs, heartbeat changes, or increase your chance of catching a cold. These effects typically last no more than a few hours, but could last longer if you are especially sensitive. No permanent health effects have been seen following exposure over short periods of time in studies like this.

A lifetime of exposure to air pollution is known to increase your risk of developing lung cancer. However, the two hours of exposure to wood smoke emissions in this study is unlikely to increase your risk in any meaningful way, just as smoking a single cigarette would carry much less risk than a lifetime of smoking.

5% Salt water inhalation (also called: Hypertonic Saline inhalation): Inhalation of the 5% salt water carries a small risk of bronchospasm, which may lead to the onset of asthma-like symptoms. This is uncommon in healthy adults without a history of underlying airway hyper-reactivity.

Lung transmission scan and Mucociliary Clearance (MCC) scan: The lung transmission and MCC scans entail exposure to radiation. The total radiation dose you will receive in this study is 177 mRem, which is equal to the radiation exposure everyone receives from natural background sources in 215 days. The risk from the radiation dose received from this procedure is too small to be detected. You must inform one of the investigators if you have had any x-rays or other radiation exposure within the past year so that we do not exceed the yearly dose limits. If you wish, Dr. Hernandez will provide you with additional information and answer any questions you

may have. If desired, additional information can be obtained from Marija Ivanovic, Ph.D, Chairman of the Radiation Safety Subcommittee of UNC Hospitals at 919-843-0717. Although it is best to avoid radiation exposure, this is a small amount of radiation and is considered acceptable to experience on a limited basis. You should take this information into consideration when agreeing to participate in this study and any future studies. The tape that is used to hold the radioactive discs (Americium 241) to your upper and lower back can cause mild irritation.

Exhaled breath condensate: There are no additional risks associated with the EBC procedure as study subjects are simply asked to exhale into a chilled tube.

Blood draw: There is a small risk of pain or bruising with blood draws. Rarely, some get light headed, so we will allow you to lie down during the blood draw. Our staff is experienced in this procedure.

Lung function: You might have the sensation of being lightheaded, or feeling faint. You will be seated in a non-rolling chair for security.

Sputum induction: This can make you short of breath, or cause you to wheeze or cough. We will monitor you closely, and we will stop the procedure if we, or you, feel that you are not tolerating the procedure.

Exercise: The moderate exercise on the bicycle could potentially cause leg cramps or soreness. We encourage you to stay well hydrated with water.

What are the risks to a pregnancy or to a nursing child?

Since radiation can be especially harmful to a developing fetus, it is important that pregnancy be avoided during this study by using effective birth control measures (either hormonal contraceptives, like birth control pills; or a barrier method, like condoms). Pregnancy tests will be done on all females who might be able to get pregnant at the start of the study and before each lung scan; these tests will be paid for by the study site. If you become pregnant during the study you should notify the researcher right away.

If you are a woman and you are planning to get pregnant, you should not be in the study. We know that radiation is harmful to an unborn baby. If you are a man, you should not father children while in the study. If you or your partner becomes pregnant during the study you should notify the researcher right away.

Pregnancy tests will be done on all females who might be able to get pregnant at the start of the study. The Center will purchase these pregnancy tests.

There may be uncommon or previously unknown risks. You should report any problems to the researcher.

What if we learn about new findings or information during the study?

You will be given any new information gained during the course of the study that might affect your willingness to continue your participation.

How will information about you be protected?

Your personal information, including your name, will go into a database called REDCap, which is designed for research studies. Only individuals who need to see your identifying information will have access to this part of the database. All study data will be coded with your study number. Any hard copy item with any personal identifying information, such as the study worksheets, will be secured in a locked office when not in use. No one outside of the study staff will have access to these records. We will need to use your date of birth for the lung function program.

Participants will not be identified in any report or publication about this study. Although every effort will be made to keep research records private, there may be times when federal or state law requires the disclosure of such records, including personal information. This is very unlikely, but if disclosure is ever required, UNC-Chapel Hill will take steps allowable by law to protect the privacy of personal information. In some cases, your information in this research study could be reviewed by representatives of the University, research sponsors, or government agencies (for example, the FDA) for purposes such as quality control or safety.

Federal law called the Genetic Information Nondiscrimination Act (GINA) generally makes it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information. GINA does not protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance. GINA also does not protect you against discrimination based on an already-diagnosed genetic condition or disease.

The study team would like to message you by e-mail, however you may say "no" to receiving these messages and still participate in this study. If you say "yes", messages may contain personal information about you and may be sent or received by the study team's personal electronic devices or in a method that is not able to be encrypted (protected) and there is the risk your information could be shared beyond you and the study team. This information may include information such as reminders and notifications to contact the study team.

If you wish to stop receiving unprotected communication from the study team or have lost access to your device, please notify the study team using the study contact information on the first page of this consent form. After the study is complete and all research activities finished, or you withdraw from the study or request to stop receiving unprotected communication, you will no longer receive un-encrypted (un-protected) messages specific to this study.

_____ Yes, I consent to the study team utilizing the following (insert mechanism; e.g. cell phone number, email) to send communication: List e-mail:

_____

_____ No, I do not consent to receive un-protected communication from the study team.

What will happen if you are injured by this research?

All research involves a chance that something bad might happen to you. This may include the risk of personal injury. In spite of all safety measures, you might develop a reaction or injury

from being in this study. If such problems occur, the researchers will help you get medical care, but any costs for the medical care will be billed to you and/or your insurance company. The University of North Carolina at Chapel Hill has not set aside funds to pay you for any such reactions or injuries, or for the related medical care. You do not give up any of your legal rights by signing this form.

What if you want to stop before your part in the study is complete?

You can withdraw from this study at any time, without penalty. The investigators also have the right to stop your participation at any time. This could be because you have had an unexpected reaction, or have failed to follow instructions, or because the entire study has been stopped.

Will you receive anything for being in this study?

You will be receiving a total of $1,115 for taking part in this study. Subjects will be paid for participation as detailed below:

Visit 0 Baseline: $35

Visit 1 & 2 - Training Day & Follow up Scan: $165

Visit 3 (Period 1) & Visit 7 (Period 2) WSP exposure: $300 (this is the payment for each visit)

Visit 4 (Period 1) & Visit 8 (Period 2) 24hrs post WSP exposure: $55 (this is the payment for each visit)

Visit 5 & 6 - Baseline & Follow up scan (Period 2): $155

Visit 9 - $ 50

Parking coupons will be provided for parking in the ACC Visitor's Parking lot or the Dogwood Visitor's Parking deck as needed.

Your name, address, and U.S. tax payer identification number (SSN or ITIN) are required to process payments and/or to report taxable income to the IRS. You must complete a W-9 (for U.S. persons) or W-8BEN and the Foreign Vendor Withholding Assessment with supporting documents (for non-resident aliens) in order to receive payment for participation.

U.S. person participants must complete Form W-9 in order to receive payment for participation. If payment by UNC equals or exceeds $600 per calendar year for U.S. persons, UNC will report the amount to the Internal Revenue Service on Form 1099. Nonresident alien participants must complete Form W-8BEN and the Foreign Vendor Withholding Assessment with supporting documents in order to receive payment for participation. Payments to nonresident alien participants may be subject to tax withholding and are generally reported to the Internal Revenue Service on Form 1042-S. This information will not be linked to any of the study data and will

only be used for payment purposes, if you do not provide your SSN (or ITIN), we cannot issue you a payment for participation. However, you may still choose to participate in this study.

You will be paid for your participation by check, we will just need to provide the w-9 form discussed above to University Accounts Payable. If you change your address, we'll need for you to complete a new form. You may have the payment directly deposited in your bank account, and we'll need your banking information to be able to do that. Please note that the checks are sent by University Accounting, so we will not be able to give it to you to at the end of your research visit. Checks may take a little longer than direct deposits, but typically can be expected via mail within ~4 weeks.

The University is seeking a vendor to work with which will allow us to give you pre-paid gift cards, pre-paid Visa or Mastercard including virtual cards. When this is available to the study team, you will have the option of being paid in this fashion.

If you do not provide your SSN or ITIN, or complete the appropriate documentation noted above, we cannot issue you a payment for participation. However, you may still choose to participate in this study.

Will it cost you anything to be in this study?
It will not cost you anything to be in this study.

What if you are a UNC student?
You may choose not to be in the study or to stop being in the study before it is over at any time. This will not affect your class standing or grades at UNC-Chapel Hill. You will not be offered or receive any special consideration if you take part in this research.

What if you are a UNC employee?
Taking part in this research is not a part of your University duties, and refusing will not affect your job. You will not be offered or receive any special job-related consideration if you take part in this research.

Who is sponsoring this study?
This research is funded by Department of Defense. This means that the research team is being paid by the sponsor for doing the study. The researchers do not, however, have a direct financial interest with the sponsor or in the final results of the study.

What if you have questions about this study?
You have the right to ask, and have answered, any questions you may have about this research. If you have questions about the study (including payments), complaints, concerns, or if a research-related injury occurs, you should contact the researchers listed on the first page of this form.

A description of this clinical trial will be available on www.clinicaltrials.gov, as required by U.S. Law. This website will not include information that can identify you. At most, the website will

include a summary of the results. You can search this website at any time.

What if you have questions about your rights as a research participant?
All research on human volunteers is reviewed by a committee that works to protect your rights and welfare. If you have questions or concerns about your rights as a research subject, or if you would like to obtain information or offer input, you may contact the Institutional Review Board at 919-966-3113 or by email to IRB_subjects@unc.edu.

Participant's Agreement:

I have read the information provided above. I have asked all the questions I have at this time. I voluntarily agree to participate in this research study.

_____ _____
Signature of Research Participant Date

_____
Printed Name of Research Participant

_____ _____
Signature of Research Team Member Obtaining Consent Date

_____
Printed Name of Research Team Member Obtaining Consent