Peripheral Vascular Effects of Sulfhydryl-containing Antihypertensive Pharmacotherapy on Microvessels in Humans

NCT03179163

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Informed Consent

CONSENT FOR RESEARCH
The Pennsylvania State University

Title of Project: Peripheral vascular effects of sulfhydryl-containing antihypertensive pharmacotherapy on microvascular function and vessel remodeling in hypertensive humans (IRB#3224)

Principal Investigator: Lacy Alexander, Ph.D.

Address: 113 Noll Laboratory, University Park, PA 16802

Lab Telephone Number: 814-863-8556

Subject's Printed Name: _____

We are asking you to be in a research study. This form gives you information about the research.

Whether or not you take part is up to you. You can choose not to take part. You can agree to take part and later change your mind. Your decision will not be held against you.

Please ask questions about anything that is unclear to you and take your time to make your choice.

1. Why is this research study being done?

Purpose: High blood pressure is a leading risk factor for cardiovascular disease (CVD). About 1/3 of the adults in the U.S. have high blood pressure. The good news is that there are treatments that lower blood pressure. These have been shown to reduce the incidence of death from CVD. They also can reduce other effects of high blood pressure and increase quality of life. Angiotensin converting enzyme inhibitors (ACEi) are a class of drug that doctors often prescribe to lower high blood pressure. A couple of ACEi also have antioxidant actions. Therefore these drugs can work through different routes to lower blood pressure. In this study, we explore how the ACEi with antioxidant actions work in a ways other than that of regular ACEi drugs.

- This project includes people with high blood pressure and those who do not have high blood pressure ("healthy controls").
    - If you do not have high blood pressure (healthy control): You perform the series of experiments. Then you repeat the experiments after 16 weeks.
    - If you have high blood pressure: You would perform in a series of experiments. Then we randomly assign you one of three drugs that doctors prescribe to lower blood pressure. The drug could be an ACEi, an ACEi that has antioxidant actions, or a diuretic ("water pill"). You would take the assigned drug for about 16 weeks to lower your blood pressure. Then you repeat the experiments. These drugs are approved by the FDA to treat high blood pressure. The research doctors prescribe the drug in this study using the dosing guidelines approved by the FDA.

Some of the experiments in this study use a research technique called "microdialysis" (MD). With MD, we perfuse some research drugs into nickel-sized areas of skin on your arm. The drugs remain in the small areas and do not go into the rest of your body. The research drugs are not approved by the FDA to treat disease. However, the FDA has approved our using the drugs in this study. We and others have used these drugs in people in research studies for many years without problem.

We are asking you to be in this research because you fit our criteria for being a subject.

About 70 people will take part in this research study in our lab. About 60 people will have high blood pressure.

2. What will happen in this research study?

You participate on the circled days or procedures. Please read the descriptions of the circled days. Then write your initials by the circled days or procedures.

We may ask you to repeat a trial, procedure, or test. This could happen for many reasons such as equipment failure, power outage, inconclusive test results, etc. You do not have to repeat a trial, procedure, and/or test if you do not wish to do so.

Sections A-E are relevant to all participants.
Section F is relevant to only those who have high blood pressure.

A. <u>Screening Visit</u>:

_____ initial 1. All Subjects Please drink only water and do not eat for 12 hours before your screening. Report to Noll Lab. The research nurse and/or Clinical Research Center (CRC) staff perform the screening. The staff measures your height and weight, blood pressure (BP), and heart rate (HR). They measure waist circumference. The staff collects your medical history. A research clinician reviews your medical history. The staff draws 30 ml (2 Tbsp) of blood from a vein in your arm. We send some of the blood to a lab to see if the proteins, blood cells, electrolytes, etc. are within normal levels. If you are a woman of childbearing age, you submit a urine sample for a pregnancy test. If you take a thyroid drug, you supply the results of a thyroid test taken within the past 6 months. If you do not have thyroid test results, the staff draws 3.5 ml (0.2 Tbsp) of blood from a vein in your arm. We send the blood to a lab that tests it for thyroid levels. The lab destroys the sample after testing. We do not do genetic tests on the blood. We do not test the blood for disease (e.g. HIV).

_____ initial 2. Subjects who have high blood pressure

If you have high blood pressure or suspect that you have high blood pressure, you perform a 24-hour blood pressure monitoring. We provide the monitor. We give you a handout that tells you about the monitor and how to use it.

> **_____ initial** If you are taking a drug prescribed by your doctor to lower your blood pressure, you may still be in the study. However, you must stop taking the drug while you are in the study. We require your doctor's permission to stop your drug. If you allow, we send two forms to your doctor. 1) Your doctor signs one form that allows you to stop your drug. 2) You sign the other form (Authorization To Use & Disclose Protected Health Information For Research Purposes")

that allows your doctor to share the first form with us. If you do not want us to contact your doctor, you withdraw from the study. If your doctor does not allow you to stop taking the drug, you withdraw from the study.

- If you stop taking a doctor-prescribed drug:
    - You take your blood pressure every 6-8 hours for 14 days washout.
    - If you are stopping a beta blocker the washout could be longer. The cardiologist working with this study decides how long the washout should be.
    - During the first week, the nurse will call you daily for you to report your blood pressure.
    - After the first week of washout, the nurse will call you every other day for you to report your blood pressure.
    - After the washout, you perform the first experiment.
    - If your blood pressure goes up too high during the washout (168 systolic or 96 diastolic)
        - Call Susan Slimak, RN (the research nurse)
        - Restart the drug prescribed by your personal doctor.
        - Withdraw from the study.
        - Follow up with your personal doctor.

B. _____ initial Blood Sample: We take a 30 ml (2 Tbsp) blood sample when you come to the lab for one of the first experiments. We analyze the blood sample for substance that are important for questions that we explore in this study. We do some of the analysis in the Noll Lab. We send some of the sample to an outside lab for other analyses. Most of the time, we use up all of the sample with the analysis. We do not do genetic tests on the blood. We do not test the blood for disease (e.g. HIV). We destroy any sample that remains after we publish the results of the study.

C. MD Experiments: The 2 types of MD experiments occur on separate days.

_____ **initial** Preparation for all MD experiments:

1) We give you printed and verbal instructions listing what you need to do before you arrive at the lab. Please follow the instructions with care and arrive prepared. If you have questions, please contact us right away.
2) You do not eat or drink anything containing caffeine (ex. coffee, tea, Coca Cola, chocolate) for 12 hours before the experiment.
3) When you arrive at the laboratory, we measure your blood pressure (BP) and heart rate (HR). We measure your oral temperature.
4) Women of childbearing age submit urine for a pregnancy test if they have not had a test within 2 weeks of the experiment.
5) Specific Preparation: Microdialysis (MD)

    a. Overview: MD involves placing very thin plastic tubing between the layers of your skin. The largest part of the tubing is about 6 times the diameter of a human hair. We pump fluid like that found in your body's tissues (lactated Ringer's solution) through the thin tubing. The thin tubing acts like the very small blood vessels in your skin. There is an exchange of substances between the fluid in the tubing and the fluid in the surrounding tissue. During the experiment, we add substances to the fluid in the tubing. The substances can only reach a 2.5 cm^2 (0.4 $inch^2$), nickel-sized area of skin.

    b. The research drugs used with MD in this study are:

- Acetycholine (ACh) – like a substance made by your body; causes blood vessels to dilate (get bigger)
- Aminoxyacetic acid (AOAA) – blocks a substance that makes blood vessels dilate
- Vitamin C – extends the life of norepinephrine in the fluid; antioxidant
- LNAME - blocks a substance made by your body that makes blood vessels dilate
- Norepinephrine (NE)— like a substance made by your body's nerves; causes blood vessels to constrict
- Sodium nitroprusside (SNP) —causes blood vessels to dilation
- Sodium Sulfide (Na_2S) – a substance that supplies hydrogen sulfide, a substance your body makes to dilate blood vessels
- Cysteine – an amino acid found in foods; used by your body in a natural process that makes hydrogen sulfide

c. MD Probe Insertion: We place a tight band around your arm so we can easily see your veins. For each MD site, we make pairs of pen-marks 2.5 cm (1 inch) apart and away from veins. The MD tubing enters and exits your skin at the marks. We remove the tight band. We clean your arm with an orange-colored fluid and alcohol. We place an ice bag on your arm for 5 minutes to numb your skin. Then we insert a thin needle into your skin at each entry mark. The needle's tip travels between the layers of skin for 2.5 cm (1 inch). It leaves your skin at the matching exit mark. We thread the MD tubing through the needle. Next, we withdraw the needle leaving the tubing in your skin. We prepare 4 MD sites in this manner. Any redness of your skin subsides in about 60 – 120 minutes.

6) We tape a thin probe and its holder over each site where there is MD tubing in your skin. The thin probe measures skin blood flow with a weak laser light. We control the temperature of the holders. The holders will start at 33°C (91.4°F). During the experiment, we measure blood pressure and heart rate.

_____ initial 1. Sodium Sulfide (Na2S) Dose Response and Local Heating MD experiment

1) We prepare 4 MD sites on your arm ("MD Probe Insertion").
2) We start the fluid flowing through the tubing on your arm while we wait for the redness to go away.
3) We perform the two parts of the experiment at the same time.

a. <u>Na2S Dose Response</u> Probe 1. Lactated Ringer's only (control)
Probe 2. Lactated Ringer's + LNAME

i. We collect second baseline data for 20 minutes.
ii. When the skin blood flow becomes stable (about 40 minutes), we add Na2S to the plain fluid flowing through each probe.
iii. Then we switch between plain fluid (about 10 minutes) and plain fluid + Na2S (about 5 minutes) in each probe. The amount of Na2S changes with each switch. You may receive up to 9 different amounts of Na2S at both probes.
iv. After the last amounts of Na2S end, we increase the skin's temperature to 43°C (109.4°F) at all MD sites. At the same time, we add SNP to all MD probes. Heating and adding SNP to the fluid help the blood vessels in your skin to dilate.
v. After about 30 minutes, the experiment ends.

b. Local Heating — Probe 3. Lactated Ringer's + Cysteine
Probe 4. Lactated Ringer's + Cysteine + AOAA

i. We collect baseline data for 20 minutes.
ii. We add the drugs to plain fluid at the MD sites.
iii. We collect second baseline data for 20 minutes.
iv. Then, we slowly increase the temperature at the MD sites to 42°C (107.6°F).
vii. When the skin blood flow becomes stable again (about 40 minutes), we stop the drugs.
viii. We increase the skin's temperature to 43°C (109.4°F) at all MD sites. At the same time, only plain fluid + SNP flows through the tubing at all sites. Heating and adding SNP to the fluid help the blood vessels in your skin to dilate.
ix. After about 30 minutes, the experiment ends.

4) We remove the MD tubing from your skin and place sterile bandages over the sites.
5) If you want, we can place a bag of ice on the sites for 10 minutes to reduce any bruising that may occur.
6) We measure your blood pressure and heart rate before you leave the lab.

_____ initial 2. Acetylcholine (ACh) and Norepinephrine (NE) Dose Response MD experiment

1) We prepare 4 MD sites on your arm ("MD Probe Insertion").
2) We start the fluid flowing through the tubing on your arm while we wait for the redness to go away.
3) We perform the two parts of the experiment at the same time.

a. ACh Dose Response — Probe 1. Lactated Ringer's only (control)
Probe 2. Lactated Ringer's + LNAME
Probe 3. Lactated Ringer's + AOAA

i. We collect baseline data for about 20 minutes.
ii. Then we add the test substances to plain fluid at MD sites 2 – 3 for 60 - 90 minutes.
ii. We collect second baseline data for 20 minutes.
iii. When the skin blood flow becomes stable (about 40 minutes), we add the first amount of ACh in the plain fluid flowing through each probe.
iv. As the skin blood flow becomes stable at each probe, we proceed to the next amount of ACh.
v. Each probe receives up to 10 increasing amounts of ACh over 70 minutes.
vi. After the last amount of ACh ends, we increase the skin's temperature to 43°C (109.4°F) at all MD sites. At the same time, we add SNP to all MD probes. Heating and adding SNP to the fluid help the blood vessels in your skin to dilate.
vii. After about 30 minutes, the experiment ends.

b. NE Dose Response — Probe 4. Lactated Ringer's only

i. We collect baseline data for about 20 minutes.
ii. We add NE to the plain fluid flowing through the probe.

iii. Then we switch between plain fluid and plain fluid + NE (about 5 minutes) in each probe. The amount of NE changes with each switch. You may receive 11 different amounts of NE.
iv. After the last amount NE ends only the Lactated Ringer's flows through the MD probe.
v. We wait for 10 minutes to let the effects of the last amount of NE to subside.
vi. We increase the skin's temperature to 43°C (109.4°F) at the MD site. At the same time, we add SNP to the MD probe. Heating and adding SNP to the fluid help the blood vessels in your skin to dilate.
vii. After about 30 minutes, the experiment ends.

4) We remove the MD tubing from your skin and place sterile bandages over the sites. If you want, we can place a bag of ice on the sites for 10 minutes to reduce any bruising that may occur.
5) We measure your blood pressure and heart rate before you leave the lab.

D. _____ initial <u>Flow Mediated Dilation (FMD) / Sublingual nitroglycerin Experiment:</u>

FMD: FMD measures the health of blood vessels.
1) We place a blood pressure cuff around your forearm.
2) We place gel on your upper arm just above the elbow.
3) We place a Doppler ultrasound probe on the gel. The ultrasound makes sound waves to measure the size of blood vessels and the speed of the blood.
4) We make a "resting" measurement before we inflate the cuff.
5) The cuff inflates for 5 minutes to stop blood flow to and from the forearm.
6) We deflate the cuff and perform a second reading for 3 minutes.

Sublingual nitroglycerin: This test also measures the health of blood vessels. Nitroglycerin causes blood vessels to dilate.
1) The nurse is present throughout the procedure.
2) You lie on a bed or recliner.
3) We apply a blood pressure cuff on your upper arm.
4) As with FMD, we use an ultrasound probe during the test. We place the probe on an artery near your elbow.
5) A nurse places a 0.4 mg nitroglycerin tablet under your tongue. Then you close your mouth right away. The tablet dissolves in 15-90 seconds. Do not swallow until the tablet dissolves. The effect lasts for 5-10 minutes.
6) You lie still for 20 minutes after you received the nitroglycerin. You remain in the lab at least 20 minutes after you receive the nitroglycerin.
7) You stay in the lab for up to 60 minutes after you received the nitroglycerin if you have a bad or very strong reaction (e.g. drop in blood pressure that lasts longer than usual). We monitor you during this time.

E. _____ initial <u>Biopsy Experiment</u>
1) We take two small pieces of skin from your arm (skin biopsy) using standard techniques.
2) First, you wash the site with soap and warm water. Then you sit in a recliner
3) We clean the top of the lidocaine-vial with alcohol. We clean the skin with alcohol. An approved clinician injects lidocaine into the skin at the biopsy sites to numb them. We wait a few minutes after injecting the lidocaine to give the drug time to work.
4) We clean the biopsy site 3 times with an alcohol pad.

5) We gently touch the site with the tip of a needle to see if you can feel anything. You may feel the slight pain of the pin-prick or only pressure. If you can feel pain, we wait a little longer. If needed, the approved clinician may add more lidocaine into the skin.
6) We use a punch-tool that looks like a screwdriver that has a round, hollow tip. The tip is 3mm (0.12 in) in diameter. The hollow tip acts like a cookie cutter. We place the tip of the punch against the skin at the biopsy site and apply mild pressure. You feel the pressure. The tip of the punch goes about 3 mm (0.12 in) into the skin. The punch collects a small piece of skin about 3mm x 2mm (0.12 in x 0.08 in).
7) We apply pressure with sterile dressing to the site to stop any bleeding.
8) We place the piece of skin into a small container.
9) We use the punch to remove the second piece of skin in the same way.
10) We apply a sterile bandage to the site.
11) We give you instructions about caring for the biopsy site.

F. _____ initial <u>Subjects with high blood pressure only</u>

1) We randomly place you into one of three treatment groups. If there is a health-reason that does not let you take a treatment, we assign you to one of the other treatments.
   a) Randomization: We assign each treatment a number. We use a web-based site to generate a list of the numbers in random order. As subjects join the study, we assign to them the treatment whose number appears next on the list.
   b) This means whichever study treatment you receive is determined purely by chance.
   c) You have a 1 in 3 chance to be assigned a certain treatment.
2) You begin taking your assigned treatment drug. The clinician adjusts the dose to that needed to lower your blood pressure. See "Risks" below for more information.
   a) The three drugs are:
      - **_____ initial** Hydrochlorothiazide (HCTZ or "water pill")
        - Typical dose: 25 mg orally once daily
        - FDA-approved for treatment of high blood pressure
      - **_____ initial** <u>Enalopril (Vasotec)</u>
        - Typical dose: initial – 5 mg orally once daily; then 10 to 40 mg per day in a single or two divided doses
        - FDA approved for treatment of high blood pressure
      - **_____ initial** Captopril
        - Typical dose: initial – 25 mg orally 2-3 daily; then 50mg 2-3 times/day
        - FDA-approved for treatment of high blood pressure.

   b) You take the drug for about 16-weeks plus the time it takes you to repeat the experiments (expect about 1 - 2 more weeks).
   c) We give you enough pills for 4 weeks at a time.
   d) If you are a woman who is not postmenopausal we give you pregnancy test supplies to take home. You perform the pregnancy test in 2 weeks at home.
   Special Note If you are a women who is not postmenopausal, you have a urine pregnancy test every two weeks during the treatment. You have a test at the monthly visits to the lab to pick up pills. Also, you will conduct a pregnancy test at home two weeks after each visit to pick up treatment pills. We supply the pregnancy test for you to use in your home. Keep this schedule of testing throughout the 16-week treatment.
2) After you start the treatment, the research nurse contacts you weekly to see if you are having problems keeping the treatment schedule and to discuss any questions.

3) After starting the treatment, you will either (1) come to the lab every 4 weeks to pick up pills or (2) if you are a man or post-menopausal woman you can choose to have the pills directly mailed by the pharmacy to your residence.

a) During the monthly visit, we check your blood pressure: either (1) we will directly take your blood pressure or (2) a blood pressure cuff device will be provided for you to take home for you to take your own blood pressure and report the results to us by telephone.

b) If you are a woman who is not postmenopausal, you have a urine pregnancy test.

c) If you are a woman who is not postmenopausal we give you pregnancy test supplies to take home. You perform the pregnancy test in 2 weeks at home.

4) At week 4 of the treatment, you have a blood draw (about 8.5 ml, 0.6 Tbsp) in addition to your regular monthly visit to pick up pills.

5) At week 8 of the treatment, you repeat the 24-hour blood pressure monitoring in addition to either your regular monthly visit to pick up pills or when the pills are directly mailed by the pharmacy to your residence.

6) At week 12: (only if you are taking the HCTZ)

a) If HCTZ fails to lower your blood pressure to our target (<140/90 mmHg), you may choose one of two options.

i) You may stop taking HCTZ for 2 weeks, and switch to one of the other two treatments for 16 more weeks or

ii) You may stop taking the HCTZ, and exit the study.

b) You do not have to continue with the study.

4) At week 16 of the treatment

a) You repeat the 24-hour blood pressure monitoring in addition to your regular monthly visit.

b) You repeat the all experiments.

c) We take another blood sample (about 8.5 ml, 0.6 Tbsp) to check potassium, BUN, and creatinine.

d) You continue the treatment until you repeat all experiments.

G. _____ initial <u>Subjects with high blood pressure only *and* were taking a physician-prescribed drug to lower blood pressure</u>

1) We randomly place you into one of three treatment groups. If there is a health-reason that does not let you take a treatment, we assign you to one of the other treatments.

a) Randomization: We assign each treatment a number. We use a web-based site to generate a list of the numbers in random order. As subjects join the study, we assign to them the treatment whose number appears next on the list.

b) This means whichever study treatment you receive is determined purely by chance.

c) You have a 1 in 3 chance to be assigned a certain treatment.

2) You begin taking your assigned treatment drug. The clinician adjusts the dose to that needed to lower your blood pressure. See "Risks" below for more information.

a) The three drugs are:

- **_____ initial** Hydrochlorothiazide (HCTZ or "water pill")
  - Typical dose: 25 mg orally once daily
  - FDA-approved for treatment of high blood pressure
- **_____ initial** <u>Enalopril (Vasotec)</u>
  - Typical dose: initial – 5 mg orally once daily; then 10 to 40 mg per day in a single or two divided doses
  - FDA approved for treatment of high blood pressure
- **_____ initial** Captopril
  - Typical dose: initial – 25 mg orally 2-3 daily; then 50mg 2-3 times/day

- FDA-approved for treatment of high blood pressure.

b) You take the drug for about 16-weeks plus the time it takes you to repeat the experiments (expect about 1 - 2 more weeks).
Special Note If you are a women who is not postmenopausal, you have a urine pregnancy test every two weeks during the treatment. You have a test when you come to the lab to pick up pills. The first two visits are 2 weeks apart. After the first month, the visits are 1 month apart. When the visits are 1 month apart, you will conduct a pregnancy test at home two weeks after each visit. We supply the pregnancy test for you to use in your home. Keep this schedule of testing throughout the 16-week treatment.

2) After you start the treatment, the research nurse contacts you weekly. You will report your blood pressure, tell her if you are having problems keeping the treatment schedule, and discuss any questions you may have.
3) After starting the treatment, you either (1) come to the lab every 2 weeks during the first month to pick up pills or (2) if you are a man or post-menopausal woman you can have the pills mailed directly to your residence by the pharmacy.
a) During the visit, we either (1) check your blood pressure or (2) a blood pressure cuff will be provided for you to take home and take your own blood pressure, in which you can report it back to us by telephone.
i) If your blood pressure is > 140/90 after 2 weeks of taking your assigned drug, we increase the dose of the drug.
b) If you are a woman who is not postmenopausal, you have a urine pregnancy test.
4) At week 4 of the treatment, you have a blood draw (about 8.5 ml, 0.6 Tbsp) in addition to your regular monthly visit to pick up pills.
i) If your blood pressure is > 140/90 after 4 weeks of taking your assigned drug, you will stop being in the study.
ii) We give pregnancy test supplies to women remaining in the study who are not postmenopausal. They perform the pregnancy test in 2 weeks at home.
5) At week 8 of the treatment, you repeat the 24-hour blood pressure monitoring in addition to either (1) your regular monthly visit to pick up pills or (2) if you are male or post-menopausal female, the pills can be directly mailed to your residence by the pharmacy.
6) At week 16 of the treatment
a) You repeat the 24-hour blood pressure monitoring in addition to your regular monthly visit.
b) You repeat the all experiments.
c) We take another blood sample (about 8.5 ml, 0.6 Tbsp) to check potassium, BUN, and creatinine.
d) You continue the treatment until you repeat all experiments."

3. What are the risks and possible discomforts from being in this research study? _____ initial All Participants:
There is a risk of loss of confidentiality if your information or your identity is obtained by someone other than the investigators, but precautions will be taken to prevent this from happening.

Microdialysis: The risks are less than that for a blood draw because microdialysis uses only a small, local area of skin. In contrast, a blood draw involves not only skin, but also large blood vessels and blood. You are likely to have some pain and bruising like that from a blood draw. However, we use ice to numb your arm when we insert the tubing. Also, the small needle reduces pain when we insert the tubing. You are not likely to have pain after the tubing is in place. You may feel a little pain when

we remove the tubing from your skin. Needles make some people feel lightheaded or cause them to faint. Although rare, the tubing could break as we remove it from the skin. Then we remove the tubing still in your skin by pulling on the other end of it. This presents no added risk for you. Even more rare, the tubing could break so that a piece of the tubing is left under your skin. In this case, we treat any tubing still in your skin like a splinter. We stop any mild bleeding with mild pressure and sterile gauze. Infection is possible. We keep the risk of infection very small by using sterile techniques and supplies like those used with blood draws. We apply a sterile bandage to the site after the experiment. We tell you how to take care of the site.

Fluid flowing through the tubing: The substances flowing through the tubing only go to a 2.5 cm^2 (0.4 $inch^2$) area of skin at each tubing site. The amount that enters the skin is very small. However, there is a chance of having a bad reaction to the substances. This reaction could produce redness, itching, rash, and/or swelling. A worse reaction could also cause fever, breathing problems, changes in pulse, convulsions, and/or fainting. We and other researchers have used these substances with microdialysis in skin. There have been no reports that these substances caused bad reactions. If a bad reaction should occur, we summon medical help.

> Lactated Ringer's Solution: This fluid is similar to the natural fluids in your skin. This fluid contains salt, potassium, lactate, and chloride. The acid content is like that your body's natural fluids. A bad reaction to this fluid is highly unlikely.
>
> ACh, AOAA, Vitamin C, Cysteine, LNAME, NE, Na_2S, SNP: These substances stop or mimic the action of your body's natural chemicals upon the blood vessels in the skin. A small amount of these substances enter the skin around the tubing. This only affects the blood flow in the vessels in that nickel-sized area of skin. The effect of these substances is gone within an hour after the experiment.

Sublingual Nitroglycerine:
The research-use of nitroglycerin for artery measurements is not an FDA-approved use of this drug. However, nitroglycerin has been used in this way in many research studies without problem. Nitroglycerin is FDA approved for the treatment of angina (heart pain). The drug is often prescribed for heart patients who have, or are at risk for, angina.

You may have some of the following reactions to the nitroglycerine

headache	lightheadedness	dry mouth	flushing
irregular heart beat	weakness	nausea	vomiting
5-10 minute drop in blood pressure	fainting	dizziness	sweating

You may also notice a sweet taste and/or tingling in your mouth while the tablet dissolves. All these effects are usually short-lived. We can reduce some of them by having you lie down for 20 minutes after you receive the tablet. If your blood pressure drops, it is likely to return to within 10 mmHg of your starting level by the time the test ends. We monitor you for up to an hour after you receive the nitroglycerin if you have a strong or bad reaction. If your blood pressure does not return to baseline, and you have related symptoms (e.g. dizziness) we advise you to see your doctor. You could have a mild or severe allergic response to the drug. This response could include rash, itching, difficulty breathing, and swelling of your face, lips, tongue, or throat. If you have a severe reaction (e.g. severe allergic response) we call 911.

The effects of nitroglycerin on pregnant or nursing women are unknown. You are not to be in the study if you are pregnant or nursing.

Laser Doppler Flowmetry: Weak lasers can hurt your eye if you stare into the light for a long time. We do not turn on the laser until the probes are taped to a surface. The tape may irritate your skin.

Blood Pressure (manual, CardioCap): The researchers measure blood pressure with the method used in a doctor's office and they can use a machine. A cuff inflates on the upper arm. As the cuff slowly deflates, the researchers listen with a stethoscope at the bend in the elbow or the machine (CardioCap) takes a reading. During the short time the researchers inflate the cuff, your arm may feel numb or tingly. The cuff could cause mild bruising.

Blood Draw: Blood draws often cause mild pain, bruising, swelling, or bleeding. There is also a slight chance of infection or a small clot. If you are nervous about needles, blood pressure and heart rate may increase for a little while. You may also feel lightheaded, sick to your stomach, or may faint. Using the same techniques used in hospitals keeps the chance of infection minimal. Do not exercise hard for 24 hours before a blood draw.

Povidone Iodine: Researchers and hospitals use this orange-colored fluid to clean the skin. You could have a bad reaction to Betadine if you are allergic to iodine. You inform us if you have this allergy. In this case, we use only alcohol instead. A bad reaction could cause redness, itching, rash, and/or swelling. A worse reaction could also cause fever, breathing problems, changes in pulse, convulsions, and/or fainting.

Tape and sticky disks: The tape or sticky disks could cause a rash. During screening, you tell us if you are sensitive to tape. If a disk sticks very strongly, removing the disk could cause an abrasion like a rug-burn on your skin. An abrasion can feel tender or slightly painful, and can increase risk of infection. If you are sensitive to tape, you may have an increased chance for abrasion. An abrasion has occurred only twice during the years that the disks have been used in similar studies in our lab. We may use an adhesive remover like that used in a doctor's office to remove the disks. If you get an abrasion a nurse checks the site. Antibiotic ointment and a sterile bandage are applied. We tell you how to take care of the site. You could have an allergic reaction to the adhesive remover. The reaction could include rash, itching, fever, or breathing problems. Also, it could include changes in pulse, and/or blood pressure, convulsions, shock, and/or fainting. If a bad reaction should occur, we summon medical help right away.

Medical Screening: You may feel shy about giving health information. The staff collects the information in a private and professional manner. You may feel shy about being measured. You may request someone of the same sex to conduct the screening.

Initial screening form: Only members of our lab group use this form. We use the form to help decide whether you are a good candidate for the study. You may feel shy about answering questions. You may request someone of the same sex to ask you the questions. We collect the information in a private and professional manner. We keep the completed confidential and secure.

Local heating: We measure the temperature of your skin under the holders. During heating, the skin feels very warm but will not hurt. The heating makes the skin under the holder red like when you take a hot bath. The redness goes away within several hours. Some people may be more sensitive to heating. If your arm feels too hot, tell us, and we reduce or stop the heating.

Skin Biopsy: You may stop the procedure at any time. Trained staff performs the biopsy. You may lie back in the reclining chair during the biopsy, if you wish. We make sure that you are informed

and ready. You may still be nervous about needles or the procedure. If so, your blood pressure and heart rate may increase for a little while. You may also feel lightheaded, sick to your stomach, or may faint. The lidocaine numbs the site so that you feel very little or no pain during the biopsy. You feel the pressure of the biopsy tool on your skin. As with any event that breaks the skin, you could get an infection. Trained staff uses sterile techniques to keep the risk of infection very small. The skin biopsy may cause some pain, swelling, bleeding, and bruising. Gauze pressed onto the site stops bleeding. An approved clinician may close the wound with a stitch. We place a sterile bandage on the site. We give you instructions about caring for the biopsy site. The biopsy is likely leave a small scar. The skin of some people overreacts to injury. If you are one of these, your skin may produce a scar that is larger and easier to see. There may be some minor pain for a couple of days when the lidocaine wears off. The pain would be like that felt after some blood draws.

Lidocaine: You may feel brief pain from the needle. You may feel brief burning when we first inject the lidocaine into the skin. Although unlikely you could have a bad reaction to the lidocaine. This reaction could produce redness, itching, rash, and/or swelling. A worse reaction could also cause fever, breathing problems, changes in pulse, convulsions, and/or fainting. If a bad reaction should occur, we summon medical help right away. If you know that you are allergic to lidocaine, we can reduce pain two other ways. We could inject sterile saline and/or use ice on the site.

Latex: Some gloves and medical materials are made of latex rubber. You will inform us if you are allergic to latex and decline to participate in the study.

FMD Test / Doppler Ultrasound: There is a small chance the probe could irritate the skin. Minor redness may occur where the researchers place the probe against the arm. This is temporary. While the researchers inflate the cuffs, the arms and feet may feel numb or tingly, and the color of the skin may change slightly. The cuffs could cause mild bruising. The gel is the same as that used with medical ultrasound tests. The gel may feel cool or cold on the skin. A bad reaction to the gel is highly unlikely.

Relevant only to people who stop taking their doctor-prescribed drugs to lower their blood pressure:

Stopping doctor-prescribed blood pressure drugs: People do not often have bad effects from abruptly stopping blood pressure medications. However, withdrawal effects can happen with stopping any blood pressure drug Most effects occur when stopping drugs that affect your central nervous system (e.g. propranolol, verapamil, clonidine). Symptoms could include agitation and headache. You could also have sweating and nausea. Less commonly your blood pressure could suddenly going up. A person who has heart disease who abruptly stops taking beta blockers could be at increased risk for chest pain, heart attack, or sudden death. If your blood pressure is > 140/90 at 4 or more weeks after starting the pharmacotherapy you will leave the study. The risk of symptoms is greater when you suddenly stop taking more than one blood pressure drug at the same time. Therefore, you will not be in the study if you are taking more than one drug prescribed by your doctor to control your blood pressure. If you are taking a beta blocker, the washout time could be longer than two weeks depending upon the dose you have been taking. The cardiologist working with this study decides how long the washout should be.

_____ initial If you have high blood pressure:

16-week Treatment Drugs: The screening helps us to find out if you have conditions under which you should not use any of these drugs. If you cannot take any of the drugs, we must exclude you

from the study. It may happen that you may not be able to take one or two of the drugs, but could take the other(s). In that case, we assign to you one of the drugs that you can take. We give you a handout with information (e.g. side effects, dosing instructions) relevant to the drug you take. If you have a side effect, you and the study doctor decide if you need medical treatment and/or you should stop being in the study. The research nurse contacts you weekly to see if you any have problems keeping up the dosing schedule. You come to the lab monthly for pill-pickup. We also check your blood pressure monthly. During the eighth week of treatment, you repeat the 24-hour blood pressure monitoring. Women who are not post-menopausal, undergo a urine pregnancy test every two weeks during treatment. Women cannot breastfeed during the treatment. You may choose to stop taking the drug and remove yourself from the study at any time.

- _____ **initial** Enalopril (Vasotec)
  This drug is the ACEi that is approved by the FDA.

  You could have a mild or severe allergic response to the drug. This response could include rash, itching, difficulty breathing, and swelling of your face, lips, tongue, or throat. Vasotec may cause the potassium in your blood to rise. If this happens, the study's physician may decide that you must stop taking the Vasotec and exit the study. The doctor prescribes doses in accordance with the FDA-approved labeling. This treatment may involve risks to an embryo or fetus, if you become pregnant. See handout for more information.

  Possible common mild side effects include:

feeling tired or weak	lightheadedness	cough
blurred vision	confusion	sweating

  More severe side effects that include:

feeling like you will faint	pounding heart beats	fluttering-feeling in your chest
slow heart rate	weak pulse	muscle weakness
tingly-feeling	ill feeling	fever
chills	painful mouth sores	painful swallowing
skin sores	flu-like symptoms	trouble breathing
reduced or no urine output	painful urination	swelling of feet or ankles
feeling tired	shortness of breath	

  Less common side effects include:

chest pain	cough producing mucus	vomiting
runny stool	fainting	nausea
sneezing	sore throat	tightness in the chest

- _____ **initial** Hydrochlorothiazide (HCTZ):
  This is the "water pill" that is approved by the FDA.

  You could have a mild or severe allergic response to the drug. This response could include rash, itching, difficulty breathing, and swelling of your face, lips, tongue, or throat. HCTZ may cause the potassium in your blood to decrease. If your potassium decreases, the clinician may instruct you to increase your dietary potassium while you are taking HCTZ. The doctor prescribes doses in accordance with the FDA-approved labeling. This treatment may involve risks to an embryo or fetus, if you become pregnant. See handout for more information.

  Possible milder side effects include:

runny stools	mild stomach pain	blurred vision	constipation

More severe side effects include

eye pain	vision problems	dry mouth/thirst.
Nausea	vomiting	rash.
feeling weak	drowsiness	restlessness
light-headedness	fast/uneven heartbeat	muscle pain or weakness
numbness	tingly feeling.	

- _____ **initial** Captopril:
  This is the ACEi with antioxidant effects that is approved by the FDA.

  You could have a mild or severe allergic response to the drug. This response could include rash, itching, difficulty breathing, and swelling of your face, lips, tongue, or throat. The doctor prescribes the dose in accordance with FDA-approved labeling.
  See handout for more information.

  Possible common side effects include:
  light-headedness flushing (warmth, redness, or tingly feeling)
  loss of taste sensation cough
  mild itching/rash numbness, tingling, or burning pain in hands/feetMore severe side effects include:
  dizziness
  reduced or increase urinating
  chest pain or pressure, pounding heartbeats, fluttering in chest
  shortness of breath (even with mild exertion), swelling, rapid weight gain
  high potassium (slow heart rate, weak pulse, muscle weakness, tingly feeling)
  sudden weakness or ill feeling, fever, chills, sore throat, painful mouth sores, pain when swallowing, skin sores, cold or flu symptoms

  Captopril can cause injury or death to the unborn baby if the medicine is taken during the second or third trimester of pregnancy. Women should use reliable birth control while taking Captopril. If you become pregnant, stop taking Captopril. Then tell your personal doctor and the researcher, and exit the study.

4. What are the possible benefits from being in this research study?

4a. What are the possible benefits to you?

You receive a screening that informs you about your health such as your current blood pressure and blood cholesterol levels. You could gain knowledge about how your body works.

4b. What are the possible benefits to others?

About 1/3 of the adults in the U.S. have high blood pressure. High blood pressure is a leading risk factor for cardiovascular disease (CVD). CVD is a major health issue in the United States. 40% of all deaths in the United States are due to CVD. This study explores how some of the treatments doctors use to lower blood pressure work. We will learn some of the intricate mechanisms that lead to the treatment-outcomes. These results expand the knowledge base for the management of high blood pressure. We plan to use the results of this study to apply for funds to pursue this area of research further. Also, the project helps to provide important experience, education, and degree-work for students of Penn State.

5. What other options are available instead of being in this research study?
You may decide not to participate in this research.

_____ initial If you have high blood pressure: Before you decide if you want to be in this research, we will discuss the other choices that are available to you. We will tell you about the possible benefits and risks of these choices. Some therapy offered in this research is available to you without taking part in this research study. Instead, you could seek treatment from a physician or choose not to be treated at all.

6. How long will you take part in this research study?

Screening (1 Visit)	less than 1.5 hour
MD Experiments (4 Visits)	5 hours each
FMD/sublingual Nitroglycerin (2 visits)	1.5 hours
Biopsy (2 visits)	less than 1 hour

(Biopsies could occur on the same day as another experiment.)

_____ initial If you have high blood pressure

Obtain pills (3 Visits)	about 15 minutes each

Total: 27.25 Hours (7-12 visits; It could take a minimum of 18 weeks to complete the study.)

If you stop taking a drug prescribed by your doctor to lower blood pressure:
In addition to the 27.25 hour described above, you measure your blood pressure for 2 weeks before the first experiment.

HCTZ non-responders only

Screening (1 Visit)	less than 1.5 hour
MD Experiments (4 Visits)	5 hours each
FMD/sublingual Nitroglycerin (2 visits)	1.5 hours
Biopsy (2 visits)	less than 1 hour
Obtain pills (6 Visits)	about 15 minutes each

Total: 28 Hours (10-15 visits; It could take a minimum of 32 weeks to complete the study.)

Note: The biopsy may occur on the same day as one of the other visits.

7. How will your privacy and confidentiality be protected if you decide to take part in this research study?
We make efforts to limit the use and sharing of your personal research information to people who have a need to review this information.

- We keep the list that matches your name with your code number in a locked file or password protected file on a computer in a room that is locked when unoccupied. Only authorized members of the lab have access to the list.
- We label your research records with your code number and keep them in a locked file or password protected computer in a room that is locked when unoccupied.
- We label your research samples with your code number. We keep the samples in a dedicated ultralow freezer in Noll Lab until analysis.

Federal law provides additional protections of your medical records and related health information. These are described in an attached document. In the event of any publication

or presentation resulting from the research, we do not share your personally identifiable information.

We do our best to keep your participation in this research study confidential to the extent permitted by law. However, it is possible that other people may find out about your participation in this research study. For example, the following people/groups may check and copy records about this research.

- The Office for Human Research Protections in the U. S. Department of Health and Human Services
- The Food and Drug Administration (FDA)
- The Institutional Review Board (a committee that reviews and approves research studies) and
- The Office for Research Protections.

Some of these records could contain information that personally identifies you. We make reasonable efforts to keep the personal information in your research record private. However, we cannot guarantee absolute confidentiality.

This research is covered by a Certificate of Confidentiality from the National Institutes of Health. The researchers with this Certificate may not disclose or use information, documents, or biospecimens that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other action, suit, or proceeding, or be used as evidence, for example, if there is a court subpoena, unless you have consented for this use. Information, documents, or biospecimens protected by this Certificate cannot be disclosed to anyone else who is not connected with the research except, if there is a federal, state, or local law that requires disclosure (such as to report child abuse or communicable diseases but not for federal, state, or local civil, criminal, administrative, legislative, or other proceedings, see below); if you have consented to the disclosure, including for your medical treatment; or if it is used for other scientific research, as allowed by federal regulations protecting research subjects.

The Certificate cannot be used to refuse a request for information from personnel of the United States federal or state government agency sponsoring the project that is needed for auditing or program evaluation by The National Institutes of Health (National Heart Lung and Blood Institute) which is funding this project or for information that must be disclosed in order to meet the requirements of the federal Food and Drug Administration (FDA). You should understand that a Certificate of Confidentiality does not prevent you from voluntarily releasing information about yourself or your involvement in this research. If you want your research information released to an insurer, medical care provider, or any other person not connected with the research, you must provide consent to allow the researchers to release it.

The Certificate of Confidentiality will not be used to prevent disclosure as required by federal, state, or local law, however we do not collect information about unlawful activity as part of this study.

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.

8. What are the costs of taking part in this research study?
8a. What will you have to pay for if you take part in this research study?
None.

8b. What happens if you are injured as a result of taking part in this research study?
In the unlikely event you become injured as a result of your participation in this study, medical care is available. It is the policy of this institution to provide neither financial compensation nor free medical treatment for research-related injury. By signing this document, you are not waiving any rights that you have against The Pennsylvania State University for injury resulting from negligence of the University or its investigators.

9. Will you be paid or receive credit to take part in this research study?

_____ **initial** If you have normal blood pressure
MD experiments: ($15.00 for each MD probe + $40 for completing an MD experiment)

Na2S Dose Response /Local Heating $200.00 ($100.00 x 2, pre and post-treatment)
ACh/NE Dose Responses $200.00 ($100.00 x 2, pre and post-treatment)
$400.00 total

Biopsy: $200.00 $50.00 each (2 pre + 2 post-treatment)

FMD/Sublingual Nitroglycerin: $100.00 $50.00 each (1 pre + 1 post-treatment)

Total = $700.00

_____ **initial** If you have high blood pressure
MD experiments: ($15.00 for each MD probe + $40 for completing an MD experiment)

Na2S Dose Response /Local Heating $200.00 ($100.00 x 2, pre and post-treatment)
ACh/NE Dose Responses $200.00 ($100.00 x 2, pre and post-treatment)
$400.00 total

Biopsy: $200.00 $50.00 each (2 pre + 2 post-treatment)

FMD/Sublingual Nitroglycerin: $100.00 $50.00 each (1 pre + 1 post-treatment)

Total = $700.00

HCTZ non-responders: Receive $60.00 for the 12 weeks on HCTZ
Switched to an ACEi $760.00 total = $700.00 (pre and post experiments) + $60.00
Not switched to an ACEi $410.00 total = $350.00 (pre experiments only) + $60.00

_____ **initial** All participants: For each trial, we pay you the amount of money equal to the part of the trial that you complete. For instance, if you complete only half of a MD experiment, we pay you for each probe that we insert plus $20.00 for that trial. This is because $20.00 is one-half of $40.00. We may ask you to repeat a trial. If you agree to repeat a trial, we pay you for the repeated trial as stated above.

We reimburse mileage for those who live 20 or more miles from Noll Lab at the rate set by current PSU policy.

We will need to record your social security number on the payment for taxation purposes.

Total payments within one calendar year that exceed $600 will require the University to report these payments to the IRS annually. This may require you to claim the compensation that you receive for participation in this study as taxable income

10. Who is paying for this research study?
The National Institutes of Health is paying for this research.

11. What are your rights if you take part in this research study?

- You do not have to be in this research.
- If you choose to be in this research, you have the right to stop at any time.
- If you decide not to be in this research or if you decide to stop at a later date, there will be no penalty or loss of benefits to which you are entitled.
- If you choose to withdraw from the study, all data collected up to the point of withdrawal will remain part of the study and may not be removed.

The person in charge of the research study or the sponsor can remove you from the research study without your approval. We remove you from the study if your blood pressure does not respond to the 16-week treatment. Other possible reasons for removal from the study include if the researcher deems that your health or behavior adversely affects the study or increases risks to you beyond those approved by the Institutional Review Board and agreed upon by you in this document. You may decline to answer certain questions. You may decide not to comply with certain procedures. However, your being in the study may be contingent upon answering these questions or complying with the procedures.

During the course of the research you will be provided with any new information that may affect your health, welfare or your decision to continue participating in this research.

12. If you have questions or concerns about this research study, whom should you call?
Please call:

- Study head, Lacy M. Alexander, Ph.D. (W: 814-867-1781, H: 814-880-9217)
- The research nurse, Susan Slimak RN (W: 814-863-8556, H: 814-237-4618)

if you:

- Have questions, complaints or concerns about the research.
- Believe you may have been harmed by being in the research study.

You may also contact the Office for Research Protections at (814) 865-1775, ORProtections@psu.edu if you:

- Have questions regarding your rights as a person in a research study.
- Have concerns or general questions about the research.
- You may also call this number if you cannot reach the research team or wish to talk to someone else about any concerns related to the research.

INFORMED CONSENT TO TAKE PART IN RESEARCH

Signature of Person Obtaining Informed Consent

Your signature below means that you have explained the research to the subject or subject representative and have answered any questions he/she has about the research.

_____	_____	_____	_____
Signature of person who explained this research	Date	Time	Printed Name

(Only approved investigators for this research may explain the research and obtain informed consent.)

Signature of Person Giving Informed Consent
Before making the decision about being in this research you should have:

- Discussed this research study with an investigator,
- Read the information in this form, and
- Had the opportunity to ask any questions you may have.

Your signature below means that you have received this information, have asked the questions you currently have about the research and those questions have been answered. You will receive a copy of the signed and dated form to keep for future reference.

Signature of Subject

By signing this consent form, you indicate that you voluntarily choose to be in this research and agree to allow your information to be used and shared as described above.

_____	_____	_____	_____
Signature of Subject	Date	Time	Printed Name