Sympathetic Mechanisms in the Cardiovascular and Metabolic Alterations of Obesity
NCT04329806
08/04/2021

Study Title: Sympathetic Mechanisms in the Cardiovascular and Metabolic Alterations of Obesity
Version Date: 7/19/21
PI: Italo Biaggioni, MD

Name of participant: _____ Age: _____

The following is given to you to tell you about this research study. Please read this form with care and ask any questions you may have about this study. Your questions will be answered. Also, you will be given a copy of this consent form.

Key Information:
The first section of this document contains some key points that the research team thought you would find important. The study is described in more detail after this section. If you do not understand something, please ask someone.

Key information about this study:
You are being asked to be in this research study because you have obesity and high blood pressure (hypertension). We want to learn more about how the autonomic nervous system regulates insulin levels, inflammation, and affects hypertension. This study will require 9 visits over 12 weeks. If you currently take blood pressure medication, we will ask you to stop taking it about 3 weeks before the first study day and to monitor your blood pressure at home. You will take one of two study drugs for 9 weeks. One of the drugs is experimental (meaning not approved by the Food and Drug Administration for this use.) Some of the risks of the study include low blood sugar, high or low blood pressure, headache, and fatigue. There will be no direct benefit to you for this study.

Detailed Information:
The rest of this document includes detailed information about this study (in addition to the information listed above).

You are being asked to be in this research study because you are obese and have high blood pressure (hypertension). We want to learn more about how the autonomic nervous system regulates insulin levels, inflammation, and affects hypertension.

You do not have to be in this research study. You may choose not to be in this study and get other treatments without changing your healthcare, services, or other rights. You can stop being in this study at any time. If we learn something new that may affect the risks or benefits of this study, you will be told so that you can decide whether you still want to be in this study. Your medical record will contain a note saying you are in a research study and may contain some research information about you. Anyone you authorize to receive your medical record will also get this information.

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Side effects and risks that you can expect if you take part in this study:

Stopping medications: may increase blood pressure. The symptoms of high blood pressure may include headache, dizziness, blurred vision, nausea, and swelling. You will be followed closely by a physician. If necessary, your medications will be restarted.

Microneurography: Having needles placed in or close to your nerves (microneurography) may be uncomfortable. In rare instances, numbness or tingling of the outside part of the lower leg may be felt for up to 7 days after the procedure. This is an uncommon side effect.

Insulin infusion: Insulin can lower your blood sugar levels, your blood potassium levels, and may cause heart rhythm changes. If any of these happen you may have a fast pulse, sweating, blurred vision, and hunger. There is also a rare possibility of seizures. If you begin to have any of these symptoms, the research nurse will give you a sugar solution to drink and potassium through your veins.

Potassium chloride: We may give you potassium through your veins while you are getting insulin, if you need it. Uncommon side effects of potassium chloride include irregular heartbeat. Some people find that potassium cases a burning sensation in their vein.

Cardiac output (rebreathing test): You may find breathing through a mouthpiece uncomfortable. There is no known risk associated with the small amount of inert gases used in this test.

Blood volume measurement (carbon monoxide rebreathing test): You may experience a mild headache and reduction of exercise capacity. The amount of carbon monoxide breathed during the test is similar to smoking a couple of cigarettes or breathing in a smoky room. It will be out of your body in 12-14 hours.

Heated blanket: Keeping your hand under the heated blanket during the study may be uncomfortable. In rare instances, the hand may become reddened or burned.

Infusion of micro-bubble contrast agent (Definity): In some people dizziness, chest pain, shortness of breath, or back pain may occur after being given the contrast agent. These symptoms appear within 1-15 minutes of being given the drug.

Tell your doctor immediately if any of these rare side effects occur - fatigue, fever, flushing, pain, muscle stiffness, fainting, rapid or slow heartbeat, high or low blood pressure, abdominal pain, nausea, diarrhea, vomiting, toothache, tongue disorder (swelling), dry mouth, stomach discomfort, pain in your joints, leg cramps, vertigo, numbness sensation, bruising, coughing, and shortness of breath.

A very serious allergic reaction to this drug is rare. However, seek immediate medical attention if you notice any symptoms of a serious allergic reaction, including: rash, itching/swelling (especially of the face/tongue/throat).

Blood Pressure Cuff: Frequent blood pressure measurements may be inconvenient. It may be uncomfortable to have an inflated cuff placed around your arm or finger or may cause bruising.

ECG: Sticky patches will be placed on your chest to record electrical activity of your heart. This may be uncomfortable and may cause skin irritation.

Body impedance: Measurements of body impedance (electrical resistance) are made using patches placed on the skin, which may be uncomfortable and may cause skin irritation, similar to ECG measurements. It delivers a very small electrical current. You will not feel this current, and there are no known risks associated with this procedure.

Amlodipine: Common risks of amlodipine include edema (swelling), low blood pressure, muscle cramps, dizziness, fatigue, fast heartbeat, nausea, and abdominal pain. Uncommon risks include rash, low heart rate, yellowing of the skin or eyes, decreased sexual drive, increased blood sugar, and insomnia.

Moxonidine: Moxonidine may cause dry mouth (very common), back pain, headache, weakness, feeling dizzy, itching or rash, nausea, vomiting or indigestion (common.) Rarely some people experience neck pain, nervousness, fainting, swelling, ringing in the ears, slow heartbeat, or low blood pressure. In very rare occasions, it may cause swelling of the face, lips, or mouth.

Scan (DEXA)
Having the DEXA scan may be inconvenient. Lying still for 5 minutes may be boring.

Endothelial Sampling
Sliding the tiny wire into your vein to collect cells from the walls may increase the chances of transient pain, bleeding, bruising, infection, or clot formation. A doctor experienced in collecting cells from your vein will perform the procedure.

Ultrasound with blood pressure cuff (FMD)
The blood pressure cuff may cause some discomfort or brief numbness in your hand and fingers while it's inflated. This will go away as soon as the cuff is released.

Risks that are not known:
Because this treatment is investigational, meaning non-FDA approved, there may be risks that we do not know about at this time.

Good effects that might result from this study:
The benefits to science and humankind that might result from this study: We may learn more about high blood pressure and new methods to treat it.

Procedures to be followed:

Visit 2
Three weeks after you have stopped your blood pressure medications, we will ask you to come for a study day having had nothing to eat or drink after midnight. We will place a small tube in your vein. If you are a woman who could become pregnant, we will ask for a urine sample to perform a pregnancy test. If you are pregnant, you will not be allowed to be in the study. We will place a small tube in your vein to take blood. We will place sticky patches on your chest to measure your electrocardiogram (ECG, a measure of your

heart's electrical activity), and we may also place sticky patches on the front of your body to measure body impedance (electrical resistance).

We will place a 24-hour blood pressure cuff on your arm. This will automatically measure your blood pressure for the next 24 hours. Measurements will be taken every 30 minutes from 6:00 am until 9:00 pm and every hour from 9:00 pm until 06:00 am. We will take blood while you are lying down and again after you have been standing for 30 minutes (about 1 teaspoon). We will slide a tiny wire into your vein to collect cells from the walls of your vein. We will do this three times.

We will record nerve signal activity. This is called microneurography. We will record the activity in the nerve located on the upper, outer part of your lower leg. First, we will stimulate the nerve (make it active) through the skin with a pencil-shaped point called an electrode. While we do this, you will notice sudden twitching or tingling feelings of the lower leg. This feeling is very mild and will go away when we stop. Once we have found the nerve, we will place two tiny, clean wire electrodes through your skin. We will change the position of the electrodes until we make a good nerve recording. These changes may take up to one hour. You will probably not notice the electrode when we are not stimulating through it, but it is important that you keep your leg still to maintain good recordings during the test.

While you are having the nerve testing, we may also ask you to breathe against pressure.

After the test, the electrodes will be removed by pulling them out of the skin. A few people have some aching at the recording site for a few days after the test. To lower the chances of any problems, you should not rub the site or perform tiring leg activity for at least 24 hours after the test.

We may measure your blood volume by rebreathing carbon monoxide. You will be asked to lie down for about 30 minutes. We will take a blood sample. You will then be asked to breathe through a mouthpiece. A small amount (about 3 tablespoons) of carbon monoxide will be added to the system. This will create a carbon monoxide level similar to a smoky room. You will breathe this gas mixture for 10 minutes. At the end of the 10 minutes, we will take another blood sample.

We will also measure your blood flow using a device called a tonometer that we will hold lightly against your skin at the point your arteries are closest to the skin in your arm. We will do an ultrasound scan of the artery in your arm. We will do this for about 30 seconds. We will then place a blood pressure cuff on your arm and inflate it for 5 minutes. When we release the cuff, we will again use the ultrasound to measure your artery for 3 minutes. This test is called flow-mediated dilation (FMD).

You will then be done for the day.

Visit 3

We will ask you to come for the study day having had nothing to eat or drink after midnight. We will place a small tube in your vein. If you are a woman who could become pregnant, we will ask for a urine sample to perform a pregnancy test. If you are pregnant, you will not be allowed to be in the study. We will place a

small tube in your vein to take blood. We will place cuff on your arm to measure your blood pressure during the day. We will place sticky patches on your chest to measure your ECG.

We will give you glucose (sugar solution in water) with a small amount of deuterium (a stable, non-radioactive form of hydrogen) in it for about 6.5 hours.

At the end of the first 2 hours, we will take a blood sample from you every 15 minutes for a total of 3 times (about ½ teaspoon each time).

We will then measure your heart rate, blood pressure, cardiac output, and forearm blood flow.

For the cardiac output measurement (rebreathing test), we will measure your heart's pumping capacity by analyzing the air that you breathe out. For this test, you will breathe normally for about 5 minutes through a mouthpiece connected to a bag that contains air and small amounts of inactive inert gases.

For the forearm blood flow measurement, a rubber cuff will be placed around your forearm to measure the flow of blood through your forearm. Two more cuffs will be placed - one just above the elbow and one just above the wrist. The elbow cuff will be connected to a meter which will measure the amount of blood flow.

We will give you a small amount of a contrast media called Definity (Perflutren) in your vein and perform an ultrasound of your arm. Definity is approved by the Food and Drug Administration (FDA) for use in imaging the heart (echocardiogram), but its use in this study is considered investigational.

Then, we will start to give you low-dose insulin infusion in a dextrose solution in your vein. Insulin is a medication that is approved by the FDA to treat diabetes. This will continue for 2 hours. We will take a blood sample (about ½ teaspoon) just before we start the infusion, then again every 5 minutes thereafter for about 44 more samples. We will measure your heart rate, blood pressure, cardiac output, forearm blood flow, and perform the ultrasound again at the end of this 2-hour period.

We will then repeat the above steps using a higher dose of insulin infusion for another 2 hours. At the end of this part of the testing, we will again give you a small amount of contrast media in your vein and again perform an ultrasound of your arm.

Blood pressure will be measured every 30 minutes for the whole the study.

The amount of blood taken during this study day will be a little more than a measuring cup.

At the end of the day, we will give you your first dose of study medication to take by mouth with a little water. You will get either amlodipine or moxonidine. Amlodipine is approved by the FDA to treat high blood pressure. Moxonidine is investigational, which means it is not approved by the FDA for this study. Neither you nor the study doctors will know which drug you are taking, but we can find out if there is a need.

We will give you a blood pressure monitor and instructions on how to use it. We will also teach you how to report your blood pressure using MyCap – a survey you can complete using your phone.

For the next 3 weeks, we will ask you to monitor your blood pressure and record it every day. We will check on you by phone. If necessary, we may ask you to come in for a visit. The study nurse may have you adjust how much of your medication you take after she consults with a cardiologist. The cardiologist and nurse will know which medication you are taking.

After we have completed the adjustment phase, you will then take your medication for 6 more weeks.

Visits 8 and 9

At the end of the six weeks, you will come for Visits 8 and 9. These will be just like Visits 2 and 3, including the flow-mediated dilation, except that visit 8 will not include a DEXA scan or an ECG.

At the end of Visit 9, you will be done with the study.

Payments for your time spent taking part in this study or expenses:
If you complete the entire study, you will be paid $800. If you do not complete the study, you will be paid $150 each for Visits 2 and 8 and $250 each for visits 3 and 9. This amount may be taxable and will be reported to the Internal Revenue Service (IRS).

Costs to you if you take part in this study:

There is no cost to you for taking part in this study.

Payment in case you are injured because of this research study:
If it is determined by Vanderbilt and the Investigator that an injury occurred as a direct result of the tests or treatments that are done for research, then you and/or your insurance will not have to pay for the cost of immediate medical care provided at Vanderbilt to treat the injury.

There are no plans for Vanderbilt to pay for any injury caused by the usual care you would normally receive for treating your illness or the costs of any additional care. There are no plans for Vanderbilt to give you money for the injury.

Who to call for any questions or in case you are injured:
If you should have any questions about this research study or if you feel you have been hurt by being a part of this study, please feel free to contact Dr. Italo Biaggioni at (615) 322-2312.

For additional information about giving consent or your rights as a person in this study, to discuss problems, concerns, and questions, or to offer input, please feel free to call the VUMC Institutional Review Board Office at (615) 322-2918 or toll free at (866) 224-8273.

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Reasons why the study doctor may take you out of this study:
You may be withdrawn from the study if the study doctors decide it is best for you or if you do not follow the instructions for the study. If the study doctors withdraw you from the study, you will be told the reason.

What will happen if you decide to stop being in this study?
If you decide to stop being part of the study, you should tell your study doctor.

Clinical Trials Registry:
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 Web site at any time.

Confidentiality:
All efforts, within reason, will be made to keep your personal information in your research record confidential but total confidentiality cannot be guaranteed. The study results will be kept in your research record for at least seven years after the study is over for as long as we need the information for the study. All the information on paper will be kept locked in a secure location. Any information kept in a computer will be through the Vanderbilt CRC data system, which has many safeguards. Only members of Dr. Biaggioni's research team will be able to see any of the information that would identify you. Any research data entered into your medical record will be kept as long as it is needed.

Vanderbilt may share your information, without identifiers, to others or use it for other research projects not listed in this form. Vanderbilt, Dr. Biaggioni and his staff will comply with any and all laws regarding the privacy of such information. There are no plans to pay you for the use or transfer of this de-identified information.

This study may have some support from the National Institutes of Health (NIH). If so, your study information is protected by a Certificate of Confidentiality. This Certificate allows us, in some cases, to refuse to give out your information even if requested using legal means.

It does not protect information that we have to report by law, such as child abuse or some infectious diseases. The Certificate does not prevent us from disclosing your information if we learn of possible harm to yourself or others, or if you need medical help.

Disclosures that you consent to in this document are not protected. This includes putting research data in the medical record or sharing research data for this study or future research. Disclosures that you make yourself are also not protected.

Privacy:
Any samples and information about you may be made available to others to use for research. To protect your privacy, we will not release your name. You will not receive any benefit as a result of the tests done on your samples. These tests may help us or other researchers learn more about the causes, risks, treatments, or how to prevent this and other health problems.

Study Results:

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Results of the study will not be released to you.

Authorization to Use/Disclose Protected Health Information
What information is being collected, used, or shared?
To do this research, we will need to collect, use, and share your private health information. By signing this document, you agree that your health care providers (including both Vanderbilt University Medical Center and others) may release your private health information to us, and that we may use any and all of your information that the study team believes it needs to conduct the study. Your private information may include things learned from the procedures described in this consent form, as well as information from your medical record (which may include information such as HIV status, drug, alcohol or STD treatment, genetic test results, or mental health treatment).

Who will see, use or share the information?
The people who may request, receive or use your private health information include the researchers and their staff. Additionally, we may share your information with other people at Vanderbilt, for example if needed for your clinical care or study oversight. By signing this form, you give permission to the research team to share your information with others outside of Vanderbilt University Medical Center. This may include the sponsor of the study and its agents or contractors, outside providers, study safety monitors, government agencies, other sites in the study, data managers and other agents and contractors used by the study team. We try to make sure that everyone who sees your information keeps it confidential, but we cannot guarantee that your information will not be shared with others. If your information is disclosed by your health care providers or the research team to others, federal and state confidentiality laws may no longer protect it.

Do you have to sign this authorization?
You do not have to sign this authorization, but if you do not, you may not join the study.

How long will your information be used or shared?
Your authorization for the collection, use, and sharing of your information does not expire. Additionally, you agree that your information may be used for similar or related future research studies.

What if you change your mind?
You may change your mind and cancel this authorization at any time. If you cancel, you must contact the Principal Investigator in writing to let them know by using the contact information provided in this consent form. Your cancellation will not affect information already collected in the study, or information that has already been shared with others before you cancelled your authorization.

Future studies:

May we contact you regarding future studies for which you may be eligible? ☐ Yes ☐ No

If you decide not to take part in this research study, it will not affect your treatment, payment or enrollment in any health plans or affect your ability to get benefits. You will get a copy of this form after it is signed.

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STATEMENT BY PERSON AGREEING TO BE IN THIS STUDY

I have read this consent form and the research study has been explained to me verbally. All my questions have been answered, and I freely and voluntarily choose to take part in this study.

Date	Signature of patient/volunteer

Consent obtained by:

Date	Signature

Time: _____ _____
Printed Name and Title