Vascular Dysfunction in Black Individuals: Roles of Nitric Oxide and Endothelin-1

NCT04770155

08/10/2021

CONSENT TO PARTICIPATE IN RESEARCH

The University of Mississippi Medical Center (UMMC)

Study Title:
Racial Differences in Cardiovascular Function: The Role of Endothelin-1

Principal Investigator:
Thales C. Barbosa, PhD

Key Information

This research study wants to learn about the regulation of the blood vessels in Black and White healthy young individuals to better understand the factors that may cause cardiovascular diseases later in life. If you participate, we will perform several research cardiovascular measurements (for example, electrocardiogram, blood pressure, blood flow, etc.) and procedures (blood vessel response, passive leg movement, handgrip, and leg exercises) and you will ingest a medicine called Bosentan and Placebo. When you receive Bosentan, you may experience minor headaches and swelling. More severe side effects of Bosentan may occur in individuals with a history of liver disease, and pregnant women. If you have a history of liver disease or are pregnant you will not be invited to participate in this study. Your participation will consist of three research clinic visits over up to 4 months. If you have questions, call Dr. Thales Barbosa at 601-984-1468.

Introduction

You are being invited to be in this experimental research study because you are a Black (i.e. African American) or White (i.e. Caucasian American) person of 18 to 35 years of age, with no known diseases, born and raised in the United States, with Black or White biological parents. Please ask us about anything in this document or that we tell you that you do not understand.

Purpose

We are doing this study to learn about potential differences in the regulation of the blood vessels between Black and White men and women. Such differences may be important because Black individuals develop cardiovascular diseases more often than White individuals. Our study will examine healthy young individuals to better understand the factors that may cause cardiovascular diseases later in life. We will collect research measurements to examine your cardiovascular system and, in two of the visits, we will give you either a medicine called Bosentan (125

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mg), or a Placebo, which does not contain any medicine in it. The order will be random, and you will have received both after the two visits.

Procedures

If you agree to participate in this study you will come to the research clinic (Clinical Research and Trials Unit at the UMMC campus) for three visits. For women: Before any research measurement or procedure occurs in any visit, we will ask you to provide a urine sample for a pregnancy test and ask questions about your most recent menstrual period.

Visit 1: We will explain the study to you and answer any questions you may have, then ask you to sign the Consent Form. We will ask you to sign a document allowing us to access your medical records to find your health information from the time when you were a newborn. We will also provide you with a document to be signed by your biological mother, allowing us to access your mother's medical records to find her health information from the time when she was pregnant with you. After that, we will ask you questions about your health, about experiences you went through during your childhood, and about your perception of social discrimination. Then, a nurse will collect a small amount (less than 10 tablespoons) of blood and cells from your vein. Next, we will demonstrate the measurements and procedures that will happen in the study and have you perform a leg exercise test. This visit will last for about 2 hours.

Visit 2: If you qualify for participation, we will schedule Visit 2 within 4 weeks after Visit 1. At the beginning of the visit, you will receive a liquid mixture (about 4 teaspoons) to be taken by mouth containing either a medicine called Bosentan (125 mg), or a Placebo that has a similar taste, color, and appearance but does not contain any medicine in it. The mixture that you will receive will be decided like "a flip of a coin", meaning that there is a 50/50 chance of receiving either Bosentan or Placebo in this visit. Two hours after taking the mixture, we will perform the research measurements and procedures as explained in detail below. This visit will last for about 4 hours.

Visit 3: We will schedule Visit 3 between 1 to 12 weeks after Visit 2. All research measurements and procedures will be identical. The only difference will be the mixture that you will take by mouth. For example, if you received Bosentan on Visit 2, you will receive Placebo on Visit 3 and vice-versa.

Summary of the Research Measurements:

- Anthropometrics: We will measure your height, weight, waist, and hip.

- Electrocardiogram: We will place adhesive patches on your chest and abdomen to measure the electrical activity of the heart, similar to what is done in the doctor's office.
- Respiration: An elastic belt will be placed around your abdomen to detect the movements caused by your respiration.
- Blood pressure: Similar to measurements taken at the doctor's office, we will place a cuff around your upper arm, and the cuff will inflate and slowly deflate several times during the study visit.
- Finger blood pressure: We will place a small cuff around one of your fingers to continuously monitor your blood pressure.
- Arm blood flow: Blood flow will be measured with an ultrasound probe gently placed and held on your arm.
- Leg blood flow: Blood flow will be measured with an ultrasound probe gently placed and held on your leg.
- Blood collection: A thin, plastic tube (catheter) will be placed by a nurse in a vein in your arm, near your elbow, for the collection of blood and cells. Blood will be used to measure endothelin-1, a molecule that helps the regulation of blood circulation through the different parts of your body.
- Health condition during pregnancy: We will look for the medical records from the time your mother was pregnant with you, and when you were a newborn. With these records, we will examine the health conditions that your mother and you may have been exposed to during that time. Some examples are nutritional problems, high blood pressure, diabetes, obesity, smoking, and alcohol consumption. We will find out the duration of your mother's pregnancy, and your body weight on the day you were born.
- Self-report psychological questionnaires: We will ask you to fill out a form answering several questions about experiences you may have gone through during your childhood, and about your perception of social discrimination.

Summary of Research Procedures

- Bosentan or Placebo: We will give you a liquid mixture to be taken by mouth upon arrival at the research clinic. Bosentan (125 mg; Tracleer, Actelion Pharmaceuticals US, San Francisco, CA) is an FDA-approved medicine used for the treatment of cardiovascular diseases such as pulmonary hypertension. In this study, we will use Bosentan because of an off-label indication that it affects the function of the blood vessels in the arms and legs. Placebo will be a mixture of similar taste, color, and appearance but without any medicine in it. Visits 2 and 3 will be identical, the only difference

will be the mixture that you will take by mouth. For example, if you received Bosentan on Visit 2, you will receive Placebo on Visit 3 and vice-versa. The order in which you will receive Bosentan or Placebo will be decided like “a flip of a coin”, meaning that there is a 50/50 chance of receiving either Bosentan or Placebo in each visit. Neither you nor the study personnel will know ahead of time what mixture you will receive in each visit. If you complete Visits 2 and 3, you will have received both Bosentan and Placebo.

- Arm blood vessel response: You will lie down on a bed with your arm extended to your side. A blood pressure cuff will be placed around your forearm. This cuff will be inflated and remain inflated for 5 minutes. We will measure your arm blood flow before inflating, and right after deflating the cuff.
- Leg blood vessel response: You will lie down on a bed with your leg slightly rotated. A blood pressure cuff will be placed around your calf. This cuff will be inflated and remain inflated for 5 minutes. We will measure your leg blood flow before inflating, and right after deflating the cuff.
- Passive leg movement: You will lie down closer to the edge of the bed, with one leg on a side table, and another leg hanging off the bed. A research person will extend and flex your leg several times.
- Handgrip exercise: You will lie down on a bed with your arm extended to your side. You will be asked to exercise your hand muscles by squeezing a metal bar connected to our computer to measure your force. Each handgrip exercise trial will last a maximum of 6 minutes or until you feel like you cannot continue. You will perform three to six handgrip exercise trials. We will measure your electrocardiogram, respiration, finger blood pressure, and arm blood flow during the trials.
- Leg exercise: You will be asked to perform the leg exercise while seated on a custom leg extension chair. You will perform low and moderate-intensity exercise bouts and will be allowed to fully recover between exercise bouts.
- Ischemia-reperfusion: You will lie down on a bed with the arms and legs extended. Then, we will do either one or both of these two procedures:
    1. We will put blood pressure cuffs around each of your legs. We will inflate the cuffs tightly and temporarily stop the blood circulation of your legs for 5 min. Then, we will deflate the cuffs for 5 min of normal blood circulation. We will repeat this process 4 times;
    2. We will put a blood pressure cuff around one of your arms. We will inflate the cuff tightly and temporarily stop the blood circulation of your arm for 20 min. Then, we will deflate the cuff for 20 min of normal blood circulation. We will do this process only once.

Length of Participation

Your participation will consist of three research clinic visits over up to 4 months.

Risks

- Electrocardiogram: You may feel minor skin irritation caused by the adhesive patches. Small amounts of skin and hair are pulled slightly when the patches are removed after the study.
- Blood pressure: You may feel minor temporary discomfort, numbness, or tingling at the fingertips during cuff inflation, which will go away after cuff release. Your arm may present some bruising at the area where the cuff is inflated, which will disappear within a few days.
- Finger blood pressure: You may feel minor numbness and/or tingling at the fingertip. It is also possible that your fingertip will become slightly bluish. We will turn off the finger cuff between the research procedures, and all these symptoms will go away.
- Blood vessel response and ischemia-reperfusion: You may feel minor temporary discomfort, numbness, or tingling at the fingertips and toes during cuff inflation, which will go away some minutes after cuff release. Your arm or leg may present some bruising at the area where the cuff is inflated, which will disappear within a few days. These procedures have been used in human research for several years without problems, and are not supposed to cause growing discomfort or pain. To make you feel as comfortable as possible, we will remind you to keep your arm or leg still during and for a few minutes after the cuff inflation. Also, we will ask you about your sensations several times to ensure you feel well. Still, please remember that you are allowed to ask to stop the cuff inflation at any time.
- Handgrip and leg exercise: You may feel minor fatigue and exhaustion.
- Bosentan:
    - Possible adverse events: No adverse events have been reported when individuals used Bosentan for just one time, like in this study. Therefore, we do not expect any adverse events. Minor effects that you may expect are headaches and swelling of ankles and legs. In patients who had to take this medicine every day for more than one month, alterations in liver function have been reported. If you have a history of liver disease, you will not participate in the study. For men: This medicine can temporarily

decrease the number of sperms produced, which are the cells used for reproduction.

- Interaction with other medications: Some types of birth control methods (for example, pills, injections, skin patches, etc.) may not work as well. If you are a woman using one of these birth control methods, you will not participate in the study.
- You should always tell the study doctor about your medical history before initiating your participation in the study. We do not know how your body might respond to Bosentan. We will discuss the risks identified above with you and the chances that they will happen. There may be risks that we do not know about at this time. Unknown problems, ranging from a mild inconvenience to some severe such as liver disease may occur. If you experience any problems you should report them immediately to the study doctor (Dr. Thales Barbosa, phone: 601-984-1468, e-mail: tbarbosa@umc.edu).

- Blood collection: The risk of infection, bruising, and occasional light-headedness during a venous blood draw is minimized by using sterile conditions under the direction of research personnel with the required training and experience with these techniques. The amount of blood drawn is 10 tablespoons or less. Any stored blood will be coded (to protect confidentiality) and frozen until analysis. The code key will be kept in a locked cabinet in Dr. Barbosa's office. Only Dr. Barbosa and the research personnel will have access to the code associated with your name.
- Self-report psychological questionnaires: Given the sensitive nature of the questions in the research surveys, you may feel some distress or discomfort. You may decline to answer any question and ask us to interrupt or end the surveys at any time. We will give you information and telephone numbers of local and national services of emotional support and counseling. If you feel or we notice that you may be in a crisis, Dr. Barbosa and the research personnel will call your emergency contact person, and facilitate transportation to emergency health care.
- Protected health information: There is a risk of unintentional disclosure of your protected health information. However, the research personnel is committed to making every effort to protect the confidentiality of your records as described here and to the extent permitted by law:
  - All paper and digital data collected from this study will be stored in a secure location on the UMMC campus and a secure UMMC server. Paper and digital files will be named using codes. Only Dr. Barbosa and

the research personnel will have access to the code associated with your name.

- If we publish or present the study results, your name will not be used. If we take pictures of the study setup, we will edit them so that your face will not be visible.
- The data collected about you for this study may be used for future research studies that are not described in this Consent document. If that occurs, the UMMC Institutional Review Board will first evaluate the use of any information that is identifiable to you, and confidentiality protection will be maintained.
- The following entities may have access to your records, but only on a need-to-know basis: the Food and Drug Administration, the UMMC Office for Human Research Protections, the UMMC Institutional Review Board, UMMC Office of Integrity and Compliance, and UMMC Office of Grants and Contracts. Study data may be submitted to regulatory agencies in other countries but you will not be identified.

Pregnancy

Studies in animals indicate that Bosentan may cause harm to an unborn fetus. The risks of Bosentan to an unborn child are unknown. You may not be pregnant, trying to become pregnant, or breastfeeding a baby while taking part in this research study. Urine pregnancy tests will be done on all women at the beginning of the study visits.

Benefits

You will not receive a direct benefit from being in this research study. We hope to learn information that may help others in the future.

Alternatives

This is not a treatment study. The alternative is not to participate in this study.

Costs

There will not be additional costs to you if you participate in this study. Bosentan will be supplied by the research funds at no cost to you. Insurance companies and other third-party payers will not be billed for research procedures.

Research-related injury

In the case of injury or illness resulting from your participation in this study, medical treatment is available to you at the University of Mississippi Medical Center. You will be charged the usual and customary charges for any such treatment you receive.

Compensation

You will receive a total of $120 in gift cards upon completion of three visits. If you withdraw from participating in Visit 3, you will receive 50% of the total. If you withdraw from participating in Visits 2 and 3, you will not receive compensation.

Voluntary Participation

Your participation is voluntary. If you decide not to participate in this study you will not suffer a penalty or loss of benefits to which you are otherwise entitled.

Withdrawal

You may choose to stop your participation in this study at any time. If you decide to withdraw the information already collected about you may still be used in this study but additional information will not be collected. Your decision to stop your participation will not affect the quality of medical care you receive at the University of Mississippi Medical Center nor your academic standing.

Confidentiality

Every effort will be made to keep the information we learn about you private. Study personnel, the Food and Drug Administration (FDA), the Office for Human Research Protections (OHRP), the University of Mississippi Medical Center's

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Institutional Review Board (IRB), Office of Integrity and Compliance, and Office of Grants and Contracts may review the study records. Study data may be submitted to regulatory agencies in other countries but you will not be identified. If study results are published your name will not be used.

Protected Health Information

Protected health information is any personal health information through which you can be identified. The information collected in this study includes your name, telephone, home address, e-mail address, date of birth, age, race and ethnicity, medical history, and pictures. By signing this consent document, you authorize Dr. Barbosa and his study personnel to collect this information and use your records as necessary for this study. Dr. Barbosa will use your information for analyses and publication of scientific findings.

The digital information collected for this study will be kept indefinitely and may be combined with information collected through other research studies or used in other studies but no information will identify you. While this study is ongoing you may not have access to the research information, but you may request it after the research is completed.

Your medical information and records, once disclosed, may be re-disclosed and may no longer be protected by the Privacy Standards of the Health Insurance Portability and Accountability Act (HIPAA), which is a federal regulation designed to protect medical information, including medical information and records created through research.

You have the right to cancel this authorization at any time by providing Dr. Barbosa with a written request to cancel the authorization. If you cancel this authorization medical information and records about you that were created before the authorization was canceled will still be used and disclosed as needed to preserve the integrity of the study.

This authorization has no expiration date. If you do not sign this consent document, you will not be allowed to participate in this study.

Number of Participants

We expect 50 participants to enroll in this study.

Questions

If you have questions about this study or need to report any problems, side effects, or injuries, please call:

Dr. Thales Barbosa
Telephone: 601-984-1468
After hours and on weekends please contact via e-mail at tbarbosa@umc.edu.

You may discuss your rights as a research participant with the Chairman of the University of Mississippi Medical Center's Institutional Review Board:
2500 North State Street, Jackson, Mississippi 39216
Telephone: 601-984-2815
Facsimile: 601-984-2961

The Institutional Review Board is a group of people not involved with this study who have reviewed the study to protect your rights.

You will be given a copy of this consent document after you sign it for your records.

STATEMENT OF PARTICIPATION

I have been told about this study and the possible risks and benefits. My participation is voluntary and I may withdraw at any time without any penalty or loss of benefits to which I am entitled, including medical care at the University of Mississippi Medical Center.
By signing this form I am not giving up any legal rights I may have.

Participant's Printed Name

Participant's Signature Date

☐ I authorize the study personnel to take pictures of the study setup.

☐ I authorize the study personnel to contact me by phone or e-mail in the future for participation in other studies.

Participant's Initials: _____

Printed Name of the Person Obtaining Consent

Signature of the Person Obtaining Consent Date

I acknowledge that the participant identified above has been entered into this study, with properly obtained informed consent.

Signature of the Principal Investigator Date

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CONSENT FOR STORAGE AND FUTURE USE OF SAMPLES

We would like to keep and store leftover samples of your blood and cells to use in future research studies.

We may use the samples to help us:

- Learn more about how blood circulation works.
- Learn more about how to identify alterations in the circulation that may cause high blood pressure and other circulatory diseases.
- Learn how to prevent or cure high blood pressure and other circulatory diseases.

Your samples will be stored in a freezer, and some information about you will be stored in Dr. Barbosa's office. The samples and information may be used by other researchers, but no identifiers will be shared and no effort will be made to reconnect or re-identify your samples.

It is your choice. You do not have to let us do this and there will be no penalty if you do not let us keep the leftover samples**.** This part of the study is optional and you can be in the study no matter what you decide.

☐ You may keep, store and use samples of my blood and cells for future research studies related to high blood pressure and other circulatory diseases.

☐ You may keep, store and use samples of my blood and cells for future research studies. The studies do not have to be related to high blood pressure and other circulatory diseases.

☐ You may not keep, store and use samples of my blood or cells for any future research studies.

_____
Printed Name of Participant

_____ _____
Signature of Participant Date

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