Informed Consent

Effect of Gut Butyrate Delivery on Blood Pressure in African Americans with Hypertension

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Study Title: Effect of Gut Butyrate Delivery on Blood Pressure in African Americans with Hypertension
Principal Investigator: Marc D. Cook (NC A&T); Ian Carroll (UNC-CH)

Concise Summary

The purpose of this research study is to determine the effect of butyrate, a short chain fatty acid produced in the gut (intestines) on blood pressure (BP). As a participant with hypertension (elevated blood pressure; systolic: 130-159 and diastolic: 80-99 mmHg) you will undergo screening that includes medical health history, physical activity behavior, and dietary habits questionnaires, blood pressure measurement and a body composition measurement on a digital scale to assess your eligibility for this study. Once screening is complete, you will be required to undergo testing on 2 separate days (7 days apart). The testing days will include submitting a fecal sample obtained by you at home, self-administer an enema, submitting to blood draw after the enema, and wearing a blood pressure monitor for 24 hours after the blood draw. This sequence will be completed twice and the sequence of enema you self-administer will be randomized to a saline enema with a very small amount of butyrate and a saline enema that contains moderate amount of butyrate. You will return the monitor on the following day and this will complete your study. The screening visit and each testing visit (2 testing visits total) will take about 1.5 hours and total study duration of about 2 weeks (14 days).

This study is for research purposes and may or may not provide benefits to you. You may receive a sense of fulfillment from personally contributing to medical knowledge about how the bacteria in your gut affect your blood pressure. The risks of this study are outlined below. However, the greatest risks include emotional distress associated with collecting your own fecal sample and self-administering an enema, pain associated with blood draw, irritation or discomfort with wearing a blood pressure monitor for 24 hrs, and loss of confidentiality. If you are interested in learning more about this study, please continue to read below.

Purpose of the Study

You have been asked to participate in a research study about the effects of the short chain fatty acid, butyrate, on blood pressure in African Americans with Hypertension. You have been asked because you are an African American between the ages of 30-50 years old and have **hypertension** (moderately elevated blood pressure; systolic: 130-159 and diastolic: 80-99 mmHg).

African Americans have hypertension (high blood pressure) more often than any other population in the United States. This makes hypertension one of the most important health concerns in the African American community. Most of the time, African Americans get hypertension at an earlier age and it causes more damage.

Recently, the bacterial make-up of the intestines (gut) has been related to elevated blood pressure. Researchers believe that specific types of bacteria that breakdown fiber and make a short chain fatty acid called butyrate may be lower in African Americans with hypertension. The only way we get butyrate in our bodies is when the bacteria make it from certain carbohydrates (fiber) in our intestines and we absorb it into our blood.

The purpose of study is to measure differences in the gut bacteria that make butyrate in the stool, and measure how much butyrate is in the blood, in African Americans with and without elevated blood pressure. To study this, we are asking you donate stool and blood

samples, self-administer one enema that contains a low amount of butyrate (5 mmol) and one enema that contains a higher and safe amount of butyrate (80 mmol) seven days apart, and wear a blood pressure monitor for up to 24 hours. ***Note*** You are being asked to act as your own control by completing the self-administration of the enemas to determine if butyrate has any effect on your blood pressure. This is the reason for completing the 2 enemas in a random order, 1 week apart. The principal investigators nor you will know the order in which you receive the enema. Your blood will be drawn to measure the amount of butyrate in your blood (before and after each enema) and you will wear a portable blood pressure monitor for up to 24 hours after each enema, which will measure your BP throughout the day.

The primary researcher involved in this study is Dr. Marc Cook from the Department of Human Performance and Leisure Studies at NC A&T and Dr. Ian Carroll in the Department of Nutrition at the University of North Carolina at Chapel Hill (UNC-CH). If you do not have a primary care physician, the physician you will be referred to Dr. Veita Bland M.D. (study physician) of the Cone Health Hospital affiliated Bland PA Clinical Hypertension Clinic at 1317 N Elm St # 7, Greensboro, NC 27401, Phone: (336) 373-1557. Please ask the staff to explain any words or information that you do not clearly understand. You may take home an unsigned copy of this consent form to think about or discuss with family or friends before making your decision. If you do not qualify for the study, none of your information obtained in the screening will be stored. Approximately 20 subjects may be involved in this research at NC A&T.

This research is sponsored by the North Carolina Translational & Clinical Sciences Institute (NC TraCS) Award # 550KR181802.

Procedures

If you qualify and choose to participate in this study, you will be asked to complete an informed consent and questionnaires providing information on your health history, physical activity, race/ethnic background demographics, and dietary habits (dietary recall), and have your blood pressure and body composition (body weight, height, fat mass, muscle mass) measured at **Visit 1**. At **Visit 2**, you will be asked to provide your home collected stool sample and 3-day dietary recall, self-administer a saline enema (control: contains 0.9% saline as you would find in the store) or a saline enema that contains sodium butyrate(experimental: contains 0.9% saline and the short-chain fatty acid butyrate at a concentration of 80 millimolar), provide blood samples, and wear a 24-hour ambulatory BP monitor for the rest of the day. At **Visit 3**, you will return the 24-hour BP monitor the day after Visit 2. At **Visit 4**, 7 days after Visit 2, you will be asked to repeat Visit 2 and complete the study by administering the other enema. At **Visit 5**, you will return the 24-hour BP monitor. At Visits 2 & 4, neither you or the research assistants will know which enema you will receive, and you will be your own control subject by performing both enemas.

Your participation is expected to take about 2 weeks. Stool samples will be obtained by you at home and brought to the laboratory, along with your 3-day dietary recall, the morning you are scheduled to perform the enema and have your blood drawn. Afterward, you will leave while wearing a portable BP monitor, wear it for the remainder of the day (24 hours) and return it to the laboratory the next day. Dr. Vieta Bland, the physician and clinical hypertension specialist, will write a prescription for the enema's and they will be made at the Custom Care Pharmacy (located at 109-A Pisgah Church Road, Greensboro, NC 27455). We will pick them

up for you and have them at your Visit 2 & 4. Enema's are commonly used to relieve constipation, but they have also been used to deliver drugs into the intestines. Our purpose in using the butyrate enema is to determine how much butyrate gets absorbed into your blood and to measure butyrate's effects on your BP. Again, the bacteria in our gut naturally produces butyrate for us, but if we have reduced bacteria in our gut that make it, this may be related to elevated BP. At Visits 3 & 5, you will receive compensation for returning the BP monitor and completing that portion of the study.
Participants in this study should:

a) Be an African American adult (man or woman) between 30 - 50 years of age with hypertension (systolic: 130-159 and diastolic: 80-99 mmHg).
b) Not taking any anti-hypertension medications (although we may enroll individuals only taking a diuretic. BP will be assessed in the morning after 24-hour fast from their medication and no medication will be taken within 24 hours of their study visit or during the study. They can resume taking the diuretic after they remove the monitor).
c) Body Mass Index of 18.5-30 kg/m^2
d) Not have any other diagnosed cardiovascular disease
e) Not exercise regularly (Participate in less than 60 minutes of exercise/week)
f) Not be pregnant or be lactating
g) Be free of active diseases that affect your intestines (i.e., chronic constipation, diarrhea, Crohn's disease, ulcerative colitis, irritable bowel syndrome, diverticulosis, stomach or duodenal ulcers, diabetes, hepatitis, HIV, and cancer)
h) Have not taken antibiotics in the past 3 months
i) Have not been regularly taking medications that impact intestinal function (i.e., laxatives, enemas, anti-diarrheal agents, narcotics, antacids, antispasmodics, antidepressants, diuretics, anticonvulsants, antibiotics, herbals, homeopathy, and home remedies)
j) Have no plans of travel out of town during the study periods.
k) Agreement to adhere to Lifestyle Considerations listed within this informed consent throughout study duration

If you agree to participate, you will be asked to avoid alcohol 48 hours before your data collection appointment and not to change your eating habits. This is because changing your diet can affect the types of bacteria found in your intestines. If you are taking medication, you will be asked to continue taking them throughout the study period.

If you qualify for the study, you will be asked to do the following:

1. Complete questionnaires about your health history, racial/ethnic background, physical activity levels, and dietary habits. If you are a woman, you will be asked to verify you are not pregnant by performing a urine pregnancy test. **Risks** associated with the questionnaires and pregnancy test: You may feel a little uncomfortable sharing your personal health information. You are free to skip any questions you do not wish to answer. If you are female and test positive during the pregnancy test you may be surprised or experience distress if you were unaware.

2. Perform body composition measurements that will be done by stepping on a scale for 2 minutes. ***Risks*** associated with this procedure are minimal. You may be embarrassed to learn what your body composition (body weight, fat mass, and lean mass) is if it is unfavorable to you. This measurement will be taken by 1 study staff member and will be confidential, just as all your data.
3. Collect a stool sample at home and bring to the laboratory at Visit 2 and 4 (which will be 1 week apart). You will be provided with everything you need to collect the sample safely. ***Risks*** associated with stool sample collection include experiencing emotional stress related to working with your own stool. Mishandling the sample can lead to infections, however, personal protection equipment will be provided, and safe hand washing technique will be taught to reduce this risk to only rare cases.
4. Donating blood samples for the assessment of circulating butyrate and other biomarkers in your blood. Blood samples will be collected by a phlebotomist or a nurse. ***Risks*** associated with a blood draw include mild pain, bleeding, bruising at the site of the draw and rarely, infection.
5. Self-administer an enema, in a random order (one at Visit 2 and one, 7 days later, at Visit 4). ***Risks*** associated with the enema include experiencing emotional stress related to performing the enema, especially if you have never done so before. We will provide you with instructions on how to perform the enema effectively. If you are uncomfortable with performing the enema, a nurse associated with the study can provide you with assistance and administer it. It is also expected that you may have a bowel movement within 10 minutes of completing the enema. You will be given access to a private bathroom after the enema. You may request to have a study nurse administer the enema.
6. Have your blood pressure monitored with a monitor you will wear for 24 hours on the day you perform the enema. ***Risks*** associated with wearing a 24-hr BP monitor include discomfort while wearing and possible loss of sleep if you are awakened during the night when measurements are recorded each hour. It is expected that you will become used to the monitor throughout the day, which will likely reduce sleep disturbances overnight. In addition, you may feel embarrassed or self-conscious while wearing the BP monitor.

Procedures and Assessments

Visit 1: Screening visit – Informed consent, questionnaires, blood pressure, and body composition

1. Medical history, physical activity, and dietary recall questionnaires: We will review the medical history questionnaire to ensure all the questions and their answers regarding your health, current medication use, medical history and exercise pattern are clear. This is done to ensure you are eligible to participate in this study. You will also fill out a physical activity readiness questionnaire (PAR-Q) to determine the amount of time you exercise currently. You will also be asked to complete a dietary food record. For this, you will record your food and beverage intake for the 5 days following the initial screening. You will be provided the paper forms to complete the records before you return to submit your samples. Pre-menopausal women will be asked to confirm they

are not pregnant by taking an over-the-counter pregnancy test we will provide. This is the only time you will be asked to take a pregnancy test.

2. Blood Pressure (BP): Blood pressure will be measured after lying down for 5 minutes undisturbed. A blood pressure cuff will be placed on the right arm and connected to an automated BP monitor that will measure your blood pressure two times (approximately 1 minute apart).
3. Body Composition: Your height and body weight measured on a scale that will determine your body weight, body fat mass, body muscle mass, and total body water. The scale requires you to stand on the scale barefoot and hold on to the machine. The test takes approximately 2 minutes to complete the measurement.

Visit 2: Measurements and Sample collection

1. Body Composition: Your body weight will be measured on a scale that will determine your body weight on the same scale as before. The test takes approximately 2 minutes to complete the measurement.
2. Stool sample collection: You will be asked to submit a stool sample you collected at home within 24-hours of this visit (collected the day before). You will also need to submit your 3-day dietary recall.
3. Blood sampling: Blood will be taken from the antecubital (forearm) vein by a phlebotomist or nurse. A small amount (about 3 tablespoons) of blood will be taken right before you complete the enema (baseline). You will have less blood taken (about 2 tablespoons) 30 minutes and 60 minutes (1 hour) after you complete the enema
4. 24-hour blood pressure monitoring: We will introduce you to the 24-hour ambulatory blood pressure monitoring device that you will be sent home with to perform the measurements. You will be fitted with a blood pressure cuff and sent home with instructions on how to use it. You will also be given instructions (verbal and written) on how to keep your blood pressure diary, where you will record your activities at the time the monitor was taking your blood pressure.

Visit 3: Return the 24-hour BP monitor. You will receive compensation at this time.

Visit 4: Repeat Visit 2 by completing the other enema.

Visit 5: Return the 24-hour BP monitor. You will receive compensation at this time.

Follow-up procedures

There are no follow-up experimental procedures after participants have completed the study. Follow-up telephone calls will be made 7 days and 30 days after participation to ask about your overall health. You will be contacted to return to the lab to receive a packet and explanation of your 24-hour ABP individual results at the end of the study. Further, you may be contacted to share the publication(s) of the results which will contain your unidentifiable data.

Risks and Discomforts

The following risks are related to your participation in this research study have been explained in above and can be reviewed at this time. Additional risks may include social risks related to confidentiality. If you are faculty or staff of NC A&T, it is likely (10-25%) that your work peers may discover that they are participating in a research study. To reduce this risk may make adjustments in scheduling your experiments (weekends if requested) to reduce any potential interactions with your work peers on campus.

To minimize the risk of breach of privacy or confidentiality, all health information and blood samples collected will be stored coded as to not be able to identify you.

If you think you are having a bad reaction during or within 1 week from the end of the study, immediately contact Dr. Marc Cook (336-285-3547, mdcook@ncat.edu).

Benefits

This study is for research purposes and may or may not provide benefits to participants. You may receive a sense of fulfillment from personally contributing to medical knowledge about ways of improving gut health and blood pressure. We hope to learn more about how specific types of bacteria in the gut affect blood pressure in African Americans.

Compensation or Costs to Study Participants

For your participation in this study, you will receive compensation totaling $300 total ($150 each time you complete an experiment and return the 24-h ABP monitor). You may decide to leave the study at any time, however, no monetary compensation will be provided unless you have donated all samples and completed BP monitoring for an experiment. This includes donating the stool sample with the 3-day dietary recall, performing an enema and donating the blood samples, and wearing and returning the portable BP monitor. You will not pay for any testing or procedures associated with this study. You will not be compensated for your travel to and from the laboratory.

Certificate of Confidentiality

What is a Certificate of Confidentiality?

This research is covered by a Certificate of Confidentiality. With this Certificate, the researchers 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 proceedings in the United States, for example, if there is a court subpoena, unless you have consented for this use. The Certificate cannot be used to refuse a request for information from personnel of a federal or state agency that is sponsoring the study for auditing or evaluation purposes or for information that must be disclosed in order to meet the requirements of the federal Food and Drug Administration (FDA).

The Certificate of Confidentiality will not be used to prevent disclosure as required by federal, state, or local law, such as mandatory reporting requirements for child abuse or neglect, disabled adult abuse or neglect, communicable diseases, injuries caused by suspected criminal violence, cancer diagnosis or benign brain or central nervous system tumors or other mandatory reporting requirement under applicable law. The Certificate of Confidentiality will

not be used if disclosure is for other scientific research, as allowed by federal regulations protecting research subjects or for any purpose you have consented to in this informed consent document.

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 an insurer, employer, or other person obtains your written consent to receive research information, then the researchers may not use the Certificate to withhold that information.

Confidentiality

Your samples will be coded with an identification number (rather than your name or initials) to maintain your confidentiality. Any questionnaires or records that identify you, and this consent form signed by you, may be inspected by the Department of Health and Human Services (DHHS) agencies, the North Carolina A&T State University and University of North Carolina Institutional Review Boards. Because of the need to release information to these parties, absolute confidentiality cannot be guaranteed. However, to the extent permitted by the applicable laws and regulations, records identifying you will be kept confidential and will not be made publicly available. In general, we will not tell anyone any information about you. The results of this study may be presented at research meetings or in publications, but your identity will not be disclosed in those presentations.

Your records will be kept in a locked cabinet in a locked office space with access limited to essential research staff. Research data collected will be transferred to a password protected excel file on a password protected laboratory computer. Access will only be given to essential research staff that will update these files. Records stored in this manner will be coded and will not be able to identify you in any way. These electronic files will be kept indefinitely. Biological specimens (blood and stool samples or bacterial DNA isolated from those stool samples) will be stored in a freezer, indefinitely. No one will be able to identify you from these samples, as they will be stored with the coded ID numbers.

Information that identifies you personally will not be released without your written permission (for example, to your primary care physician), and if the results of this research are published or discussed in conferences, no information will be included that would reveal your identity. We are required to keep all data and records for at least four years after the close of the study. All paper records that may identify you as a participant in the study will be destroyed (via shredding) at that time.

Questions about the Study

If you have any questions about your involvement in this project, you may contact Dr. Cook at 336-285-3547 or by email at mdcook@ncat.edu. If you have any study-related concerns or any questions about your rights as a research study participant, you may contact the Office of Research Compliance and Ethics at North Carolina A&T State University at 336-285-2961.

Voluntary Participation/Withdrawal

Your participation is voluntary, and you may end your participation at any time. Refusing to participate or leaving the study at a later time will not result in any penalty or loss of benefits to which you are entitled.

Statement of Consent

I have read the above information and have received answers to any questions I had. I am at least 18 years of age or older and voluntarily consent to take part in this research study.

Participant's Name (Printed): _____

Participant's Signature: _____ Date: _____

Researcher's Signature: _____ Date: _____