Official Title: Ketones in Heart Failure With Reduced Ejection Fraction

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Duke University Health System

Consent to Participate in a Research Study
ADULT
Acute effects of ketones in heart failure

Principal Investigator: ***Senthil Selvaraj, MD, MS, MA.***

CONCISE SUMMARY
This research study is being conducted to test whether a ketone ester drink (DeltaG) will improve exercise in people with heart failure (HF).

The study has three visits, including a baseline visit and 2 subsequent visits where you will receive a ketone ester drink or a placebo. At each visit, participants will be served a light meal with the study drink and will undergo exercise tests, ultrasounds of your heart, have blood drawn through an intravenous line, have pressure measured non-invasively in your arteries, and as an optional test, a muscle biopsy of the leg.

Risks of exercise includes high or low blood pressure with lightheadedness as well as abnormal heart rhythms. Bleeding and physical discomfort can result from the blood draw. There is a chance of stomach irritability after ingesting the drink. If you choose to participate in the optional muscle biopsy, the risks include bleeding, soreness, and infection.

If you are interested in learning more about this study, please continue reading below.

You are being asked to take part in this research study because you have heart failure. Research studies are voluntary and include only people who choose to take part. Please read this consent form carefully and take your time making your decision. As your study doctor or study staff discusses this consent form with you, please ask him/her to explain any words or information that you do not clearly understand. We encourage you to talk with your family and friends before you decide to take part in this research study. The nature of the study, risks, inconveniences, discomforts, and other important information about the study are listed below.

The research study is being conducted to test whether a ketone ester drink (DeltaG) will improve exercise in people with heart failure (HF). In HF, patients are limited in their ability to do all the things they want to do, and exercise as much as they would like, due to becoming tired and short of breath early. We do not know exactly why these limitations occur and therefore we are trying to see is a ketone ester drink (DeltaG) will help improve exercise.

If you agree to participate, this study includes a total of 3 visits. For these, come fasting for 3 nearly full day study visits where we perform ultrasounds of the chest, (echocardiography), assess the electrical system of the heart (electrocardiography), measure pressure non-invasively on the arteries (arterial

tonometry), exercise tests on a bicycle (cardiopulmonary exercise testing), assess oxygenation of the muscle (NIRS), and possibly sample a piece of your thigh muscle (muscle biopsy). At 1 of these 3 visits, we will give you a ketone drink (DeltaG) before you exercise, and at 1 of these 3 visits, we will give you a placebo (ketone-free solution). The other visit will primarily consist of exercise without the study drink (baseline visit).

The study will last for the duration of 3 visits, which we expect will last approximately 3-4 weeks though this may be longer pending scheduling availability. Each visit will last about 5-7 hours but may be longer. This study does not have follow-up between each visit or after the 3 study visits are completed.

You are unlikely to benefit significantly from this study, since the study drink (DeltaG) lasts for a short time in the body. The most common risks of participation are related to the drink (DeltaG), which include bitter taste and stomach upset (nausea, diarrhea, constipation). There are some risks associated with performing exercise, which include high or low blood pressure with lightheadedness as well as abnormal heart rhythms. The risks of the muscle biopsy are very low (roughly 1 in 500 biopsies) and the risks include bleeding and infection.

Your participation is voluntary, and therefore you can choose to decline participation at any time. Any of your study information, including blood samples, may be sent to collaborators within and outside of Duke for analysis (including companies), though your name or identifying information will not be included. The use of DeltaG in this study is experimental. DeltaG has not been approved by the Food and Drug Administration (FDA) for the use being evaluated in this study.

Please note that there are other factors to consider before agreeing to participate such as additional procedures, use of your personal information, costs, and other possible risks not discussed here. If you are interested in participating, a member of the study team will review the full information with you. You are free to decline or stop participation at any time during or after the initial consenting process.

Please tell the study doctor or study staff if you are taking part in another research study.

Dr. Senthil Selvaraj will conduct the study and it is funded by the National Institutes of Health and American Heart Association. The sponsor of this study, National Institutes of Health and American Heart Association, will pay Duke University to perform this research, and these funds may reimburse part of Dr. Selvaraj's salary.

WHO WILL BE MY DOCTOR ON THIS STUDY?

If you decide to participate, ***Dr. Selvaraj*** will be your doctor for the study and will be in contact with your regular health care provider throughout the time that you are in the study and afterwards, if needed.

Duke University Health System

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WHY IS THIS STUDY BEING DONE?

The purpose of this study is to test the effect of a ketone ester drink (DeltaG) compared to placebo on exercise in people with HF. In HF, patients are limited in their ability to do all the things they want to do, and exercise as much as they would like, due to becoming tired and short of breath early. We do not know exactly why these limitations occur.

There is some evidence that in addition to problems with the heart, patients with HF also have problems with their arteries, liver, and muscles that affect their ability to exercise. Ketones have been shown to improve exercise capacity in healthy volunteers. An infusion of ketones through an IV line has also been shown to significantly improve heart function, but whether a drink can produce similar improvements in HF patients is unknown. This specific drink is available over the counter and given "generally regarded as safe" status by Food and Drug Administration.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

25 people will take part in this study at Duke.

WHAT IS INVOLVED IN THE STUDY?

If you participate in this study, you will be asked sign and date this consent form. You will then be asked to come to the research center at the Center for Living for 3 visits.

This study is a crossover clinical trial, which means that all participants will receive the "active" study drink for one visit, and all participants will also receive "Placebo," for one of the visits. The placebo that we will use will be a water-based drink with a bitter flavor since the "active" study drink also has a bitter taste. Neither you, nor the study investigators, will know which drink you are getting at which time. However, we can always get this information from the research pharmacy if we need to for an emergency. You can request to leave the study at any time.

Before the study begins, you may come to the research space at the Center for Living for a "familiarization" visit. This is optional and not a formal study visit. The goal is to acquaint you with the space and equipment, while also giving you a sense of what we will be doing during this visit. During this time, you may perform several tests related to light or moderate intensity exercise, heart function, and artery function. These tests are similar to the testing we will do at following visits. This may also allow you and our team to identify challenges in performing these tests during the following study visits. We may also draw blood (approximately 10 mLs) during this time for laboratory work to see if you are eligible for the study.

During the study visits (3 visits total), you will be asked to perform several tests related to exercise, heart function, and artery function, which will be discussed below. During the first visit, we will ask you some questions to ensure you are eligible for the study. We will also review your medical record

beforehand. We will ask you to exercise on a bicycle so we can understand your exercise tolerance. This exercise will involve you exercising as hard as you can one time, and then after a rest, we will ask you to exercise for as long as you can but at a lower workload (less resistance, meaning less hard to pedal). At your next study visit (Visit 2), we will give you either the ketone drink or a placebo drink and perform the same tests as during Visit 1. You will be randomly assigned (like the flip of a coin) to receive either the ketone drink or placebo at this first visit. You have a 1/2 chance of receiving ketone drink at the first visit.

After Visit 2, you will not take any study drink for ~1 week to allow the study drink to wash out of your system ***(Washout Period)***. After this period, you will be asked to come in and repeat the tests for another visit (Visit 3), in which you will receive the other drink you didn't receive previously. In this way, every participant gets a placebo drink at one visit and a ketone drink at the other.

Procedures and Visit Schedule

Prior to the study – our study team may contact you to discuss the study, ask you questions related to your health, and to make sure you are eligible for the study. You may also come for an informal, optional "familiarization" visit (before Visit 1) to see the space and do some testing related to exercise, heart function, and artery function.

Visit 1: *In-person visit at our research center. This visit will be approximately 5 to 7 hours. Please come fasting (nothing to eat after the midnight the day before). Please avoid caffeine or alcohol intake for 24 hours prior to this visit and strenuous exercise for 24 hours prior as well.*

On this first visit, we will ask you questions about your heart failure symptoms, medical history, and any medications that you are currently taking. We will draw blood before we ask you to exercise.

Here is a list of the events for Visit #1:

- *Review and sign this informed consent form.*
- *Meals* – a light breakfast and lunch will be served.
- *Vital Signs and focused physical exam* – We will check your vital signs and may perform a physical exam
- *Blood Draw* - We will draw blood from you. Blood will be drawn by inserting a needle into a vein in your arm. We will measure various substances in the blood that include, for example, hormones, ketone levels, metabolites, proteins, and the pressures in your heart. We will draw in total approximately 50-100 mL of blood (in comparison, blood donation generally involves 500 mL of blood).
- *Questionnaires* – We will give you a questionnaire that asks you questions about your symptoms.
- *Doppler Echocardiogram* - This procedure is similar to previous echocardiograms that you may have had. In this procedure we put some gel on the skin on the left side of your chest and use a

probe to take pictures of the heart and blood vessels. We may also take pictures of your lungs as well. This takes approximately 45 minutes. We will do this several times during the course of the day – before and during exercise. We will do this if we have the equipment available.

- *Cardiopulmonary Exercise Test (CPET)* - A Cardiopulmonary Exercise Test (CPET) measures how well your heart, lungs, and muscles work together to support your overall exercise performance. You will be asked to ride a bicycle ergometer while connected to an ECG machine and a blood pressure cuff. You will also be wearing a face mask that measures the amount of air that you breathe in and out. The bike will add more resistance to the pedals as you continue to bike. You will continue to exercise until you are unable to continue because of fatigue, shortness of breath, or other limiting symptoms. You can request to stop the test at any time, though we would like you to push yourself as hard as you can. Study staff will ask you how you are doing throughout the test. They may ask you to stop even if you feel that you could continue. While you are exercising, we will assess how much blood your heart is pumping during this exercise test. We may also take pulse recordings from your wrist, neck, and leg (groin). We will draw blood from your IV while you are exercising. We will ask you to exercise twice during each visit in the exercise unit. The first exercise test will be "maximal", meaning that the amount of resistance you peddle against keeps increasing every few minutes until you cannot continue and need to stop. *We would like you to push yourself as hard as possible during this test and give us your best effort.* ~1.5-2 hours after the maximal test, you will have a "submaximal" test, meaning that the amount of resistance you peddle against on the bicycle will not be as much as in the "maximal" test. You will peddle for as long as you can until you are tired and need to stop.
- *Heart rate variability* – During this procedure, we will place electrodes (stickers) on your chest to capture the electrical signals from the heart and measure the change in your heart rate while you rest. We will perform this if the machine is available.
- *Arterial Tonometry* - This is a simple non-invasive test in which we will examine the pressure in your blood vessels of your wrist, neck, and leg (groin). This test will allow us to determine how stiff your arteries are and to measure the pressure the heart is pumping against. This test will be done by a trained member of our team over approximately 30 minutes. Sticker-like electrodes will be placed over your skin on the chest to measure the electrical current generated by your heart. Next, the investigator will gently put the tonometer, which looks like a pencil, against these vessels. We will do a few times over the course of the day, both at rest and during exercise. We will perform this if the machine is available.
- Muscle biopsy – If you agree, we will sample a small piece of muscle from your thigh (muscle biopsy). If you participate in this, you will be instructed not to consume any blood thinners. If you are unsure as to whether a medication you intend to take is a blood thinner, it is strongly advised that you call the study coordinator before taking the medication. If you take aspirin, clopidogrel, ticagrelor, or prasugrel, we will ask you to hold these 3 days prior to the visits. Medications like ibuprofen or naproxen (NSAIDs) should not be taken 3 days prior to the visits. If you are on anticoagulants (such as dabigatran, apixaban, edoxaban, or rivaroxaban), we will ask you to hold these for 3 days prior to the visit, and if you take warfarin, we would ask you to

hold this for 5 days prior to the visit. We will ask your doctor for permission prior to asking you to stop these medications. A trained provider will perform the needle biopsy procedure, which involves the removal and examination of a piece of muscle tissue. The muscle biopsy will be obtained under local anesthesia. A small incision (about 1 cm) is made into the skin and fascia. To take a biopsy, a needle is then inserted into the muscle. A small "plug" of tissue remains in the needle when it is removed from the muscle. This is about the size of 2-3 grains of rice. More than one needle insertion may be needed to obtain a large enough specimen for testing and examination. The muscle that we will biopsy is the thigh muscle. You will feel some pressure or "tugging" sensations. Many people experience mild discomfort, but some subjects find the biopsy procedure painful. If there is pain, the physician will provide more anesthetic to the area to reduce the pain. The anesthetic (Lidocaine (like Novocaine) may burn or sting when injected (before the area becomes numb). After the anesthetic wears off, the area may be sore for about a week and may limit your activity.

- Muscle oxygenation (NIRS) - We will test how well your leg muscles use oxygen using a process called Near-Infrared Spectroscopy (NIRS), which measures muscle oxygen usage and will not cause discomfort. This is a non-invasive procedure, and we will perform this if the equipment is available.
- Muscle ultrasound- We will test the quality and size of your leg muscle using an ultrasound wand on the surface of your skin. This is a non-invasive procedure, it will not cause discomfort, and we will perform this if the equipment is available. This would be completed both before and after your two exercise tests.

Visit 2: *In person visit at our research center. This visit will take one day. The day before, please avoid caffeine or alcohol intake. Please avoid strenuous activity for 24 hours as well beforehand. Please come fasting (nothing to eat after the midnight the day before). Try to have a similar dinner for the meal before Visit 2 as you did prior to Visit 1. We will aim to perform Visit 2 within 2 weeks of Visit 1. We will provide a light breakfast and lunch on the visit day.*
On the second visit, we will give you the study drink or placebo and perform tests before and after.

- *Blood Draw from an IV*. Blood will be drawn by inserting a needle into a vein in your arm. We will measure various substances in the blood that tell us about your cholesterol, sugar, hormones, ketone levels, and the pressures in your heart. We will draw blood several times throughout the day as we check these levels which may change with the drink and exercise. We will draw in total approximately 200 mL of blood (in comparison, blood donation generally involves 500 mL of blood).
- *Meals* – a light breakfast and lunch will be served.
- *Randomization* - You will be randomly assigned to receive either DeltaG or placebo first. You will not be told which drink you are getting. The investigators will not know which drink you are

getting, but we can find out if needed, in the case of an emergency. You will get this twice: once before the "maximal" exercise test (where you exercise as much as you can as the test continues to get harder) and once before the "submaximal" exercise test (meaning that the amount of resistance you peddle against on the bicycle will not be as much as the "maximal" test).

- *Heart rate variability*. We will perform this if the machine is available.
- *Arterial Tonometry*. We will perform this if the machine is available.
- *Doppler Echocardiogram* and lung ultrasound. We will perform this if the machine is available.
- *Stable isotope infusion* – Stable isotopes are naturally occurring molecules that allow us to track the production and elimination of sugar (glucose) from blood samples. These are non-radioactive, and there are no known risks associated with stable isotope infusion as we plan to use in this study. We will infuse these glucose isotopes before and during the second ("submaximal") exercise test using an additional IV, and we will collect a few more blood samples). This will be done if the supplies are available and we can place an additional IV in your other arm.
- *Cardiopulmonary Exercise Test (CPET)* – you will have 2 exercise tests performed. The first exercise test will be "maximal", meaning that the amount of resistance you peddle against keeps increasing every few minutes until you cannot continue and need to stop. *We would like you to push yourself as hard as possible during this test and give us your best effort.* 1-2 hours after the maximal test, you will have a "submaximal" test, meaning that the amount of resistance you peddle against on the bicycle will not be as much as in the "maximal" test. You will peddle for as long as you can until you are tired and need to stop.
- Muscle biopsy – *if you agree and the materials are available*
- Muscle oxygenation (NIRS) - We will perform this if the equipment is available.
- Muscle ultrasound- We will perform this if the equipment is available with the same details as provided above.

If there are scheduling conflicts or you are tired, we may bring you back for a separate visit to do the submaximal exercise test, though we will try to do both tests on the same day.

At the end of this visit, we will also assess for symptoms related to the drink.

~1-week washout period: following the completion of the studies during your second visit, we will wait about 1 week to bring you back to ensure there is no study drink in your system, though we anticipate this will leave your body within several hours. You should continue all of your other regularly-prescribed medications.

Visit 3*: This visit will occur approximately 1 week after your second visit. This visit will also last about a day. The day before, please avoid caffeine or alcohol intake. Please avoid strenuous activity for 24 hours beforehand. Please come fasting (nothing to eat after the midnight the day before). Try to have a*

similar dinner for the meal before Visit 3 as you did prior to Visit 2. We will provide a light breakfast and lunch on the visit day.

Visit 3 is very similar to visit 2, except for a small difference. We will give you the opposite study drink to what you got during Visit 2 (DeltaG or placebo). In this way, every participant in the study will receive both DeltaG and Placebo, though the participants may receive these study drinks in a different order. The same testing may be performed as in Visit 2, including:

- *Vital Signs*
- *Blood Draws from IV*
- *Heart rate variability.* We will perform this if the machine is available.
- *Arterial Tonometry.* We will perform this if the machine is available.
- *Doppler Echocardiogram and lung ultrasound.* We will perform this if the machine is available.
- *Stable isotope infusion.* We will perform this if supplies available and can place an IV in your other hand.
- *CPET (maximal and submaximal tests)*
- *Muscle biopsy (if you agree)*
- *NIRs.* We will perform this if the machine is available.
- *Muscle ultrasound*- We will perform this if the equipment is available with the same details as provided above.

At the end of this visit, you will be given a survey to ask your thoughts on what order you think you received the study interventions (DeltaG first or second). We will also assess for symptoms related to the study drink.

After this, your participation in the research study will be over.

The study chart below explains what is expected of you at each study visit:

Clinical Trial: Visit 1	• Read and sign this informed consent form (**ICF**). • If you are a pre-menopausal woman who has not had a hysterectomy, we will **confirm that you are not pregnant** using a urine pregnancy test. • Complete a questionnaire about your heart failure symptoms • Have **blood drawn at rest and during exercise** from an IV. • Record **vital signs.**

Duke University Health System

Consent to Participate in a Research Study
ADULT
Acute effects of ketones in heart failure

	• Review your medications, medical history, and symptoms with the study team, and answer survey questions • **Have 2 Cardiopulmonary Exercise Tests: maximal effort and a submaximal (less resistance) exercise test** • **May have pictures of your heart (and possibly lung) taken at rest and during exercise using ultrasound (echocardiography).** • May have **arterial Tonometry** test before and during exercise • May have **a Heart Rate Variability** test • May have **a muscle biopsy** test • May assess **muscle oxygenation (NIRS)** • May complete muscle ultrasound before and after exercise tests
Clinical Trial: Visit 2 (within ~2 weeks after Visit 1)	• Have **1-2 IVs placed and have blood drawn several times throughout the testing** • Answer questions **on any changes in your medical history or medications since last visit** • **Drink the study drink** (either DeltaG or placebo) twice (once before the maximal exercise test, and once before the submaximal exercise test) • May have **Heart Rate Variability testing** • May have **Arterial Tonometry** test before and during exercise • May have an **Echocardiogram** test several times at rest and during exercise (and possibly lung ultrasound). • **Have two Cardiopulmonary Exercise Tests** (a "maximal" and "submaximal" test each) • May have a **stable isotope infusion of glucose** • May have a **muscle biopsy** • May assess **muscle oxygenation (NIRS)** • May complete muscle ultrasound before and after exercise tests

Duke University Health System

Consent to Participate in a Research Study
ADULT
Acute effects of ketones in heart failure

Clinical Trial: Visit 3 (at least 1 week after Visit 2)	• Have **1-2 IVs placed and have blood drawn several times throughout the testing** • Answers questions **on any changes in your medical history or medications since last visit** • **Drink the other study drink you previously did not receive** (either DeltaG or placebo) • Have **Heart Rate Variability testing** • The **Arterial Tonometry** test before and during exercise • May have an **Echocardiogram** test several times at rest and during exercise and possibly lung ultrasound. • May have a **stable isotope infusion of glucose,** • **Have two Cardiopulmonary Exercise Tests** (a "maximal" and "submaximal" test each) • May have a **muscle biopsy** • May assess **muscle oxygenation (NIRS)** • May complete muscle ultrasound before and after exercise tests **Your formal participation in the main study is now complete.**

If you do not sign this consent form, you will continue to receive care, but not as a part of this study.

HOW LONG WILL I BE IN THIS STUDY?

If you agree to participate in this study, you will be involved with this study for 3 visits. The clinical trial will occur over roughly 3-5 weeks though your participation may be longer pending scheduling availability.

You can choose to stop participating at any time without penalty or loss of any benefits to which you are entitled. However, if you decide to stop participating in the study, we encourage you to talk to your doctor first.

WHAT ARE THE RISKS OF THE STUDY?

***Study Drink** – Ketone ester ((R)-3-Hydroxybutyl (R)-3-Hydroxybutyrate)*

Currently, we do not have much information regarding possible side effects of DeltaG in patients with

heart failure. In studies of generally healthy individuals and one in patients with heart failure, DeltaG given as a drink was generally well tolerated.

DeltaG may cause some, all or none of the side-effects listed below.

More likely

- Stomach ache
- Nausea

Less Likely

- Vomiting
- Diarrhea or constipation
- Dizziness
- Headache
- Fatigue

In this study, you will only be given at most 2 doses of study drink on a study day, which we think will minimize the chances of significant side effects.

If you experience any side effects that you find too uncomfortable, you may withdraw from the study at any time.

Potential Drug Interactions and Instructions During the Study
There is not much information on DeltaG in subjects with heart failure. Certain medications that heart failure patients may be on (SGLT2 inhibitors such as dapagliflozin, canagliflozin, and empagliflozin) also very mildly raise ketone levels, though levels are largely still within "normal" levels. Sometimes a very high level of ketones from SGLT2 inhibitors can cause acid to build up in the blood, but this is very rare with SGLT2 inhibitors and we do not believe this risk of sustained high acid levels is increased by taking DeltaG.

For your safety, you must tell the study doctor or nurse about all the prescribed medical foods and drugs, herbal products, over-the-counter (OTC) drugs, vitamins, natural remedies, and alcohol that you are taking before you start the study and before starting to take any of these products while you are on the study.

Drug Interaction and Instructions Summary:

For the clinical trial visits: continue taking your regularly scheduled medications, including SGLT2 inhibitors. Please come to each study visit while fasting (nothing to eat or drink after midnight the night prior). Please avoid caffeine and alcohol for 24 hrs prior to each visit for the

clinical trial. Please avoid strenuous exercise for 24 hours prior to each visit for the clinical trial

Possible Risks or Discomforts of Study Procedures

Arterial Tonometry

- Minor discomfort may occur when the tonometer is placed against your neck, arm, wrist or groin. This will feel like someone is taking your pulse at these locations.
- We will use adhesive electrodes attached to your skin. These may occasionally cause itching and irritation in your skin.

Doppler Echocardiogram and Lung Ultrasound

- We will use adhesive electrodes attached to your skin. These may occasionally cause itching and irritation in your skin.
- Minor discomfort may occur when the probe is placed on your chest to obtain pictures of your heart.

Heart Rate Variability

- We will use adhesive electrodes attached to your skin. These may occasionally cause itching and irritation in your skin.

Cardiopulmonary Exercise Test

- Cardiopulmonary exercise testing involves stages of increasing physical effort. Some of the risks associated with this type of testing are abnormal blood pressure, fainting, disorders of heart rhythm, and in very rare instances, heart attack. During the test, most people just get tired. Some get short of breath or have leg pain. Some people get chest pain or discomfort. The mask, the electrodes (sticky pads) on your skin, and the pressure cuff may cause skin irritation (including development of a rash or puffiness), or potentially could involve irritation to your mouth and trachea (windpipe). Study staff will monitor you before and during testing for safety. They will stop the test if they feel it is not safe for you to continue. You may stop the test at any time and should tell the doctor and other study staff if you feel very uncomfortable during the test. There is no increased risk of exercising in our study lab, as opposed to if you were to exercise on your own, though you will be monitored when you exercise with our group.

Blood Draw

- There may be minor discomfort or pain (sometimes accompanied by redness, swelling, and warmth to the area) from the needle used to place the IV line. Some bleeding or bruising may occur. Fainting and infection at the site of the IV are both possible, although these occurrences are unlikely. You may develop inflammation in the vein where the IV was placed (superficial phlebitis) or a clot in the vein. These problems generally resolve over time on their own after the IV has been removed.

Duke University Health System

Consent to Participate in a Research Study
ADULT
Acute effects of ketones in heart failure

- Risks associated with drawing blood from your arm include momentary discomfort and/or bruising. Infection, excess bleeding, clotting, or fainting are also possible, although unlikely.

Stable isotopes

- There are no known risks associated with the use of isotopes in our study. Since we are infusing glucose into your vein, there is the theoretical risk of infection. Solutions will be made by the Investigational Drug Pharmacy and tested as appropriate for bacteria prior to their use.

Confidentiality

- There is a potential risk of loss of confidentiality. Every effort will be made to keep your information confidential; however, this cannot be guaranteed. Some of the questions we will ask you as part of this study may make you feel uncomfortable. You may refuse to answer any of the questions and you may take a break at any time during the study. You may stop your participation in this study at any time.
- If any of your data (including but not limited to blood samples, echocardiographic images, gas exchange data, and heart rate variability data) are shared with other investigators (at Duke or elsewhere), we will make sure that no identifying information is included, and that all shared samples will be de-identified. Deidentified data may be made publicly available. Any for-profit companies receiving your de-identified samples may ultimately discover products, drugs, tests, etc., as a result of this research and your samples. This discovery may lead to commercial products, and you would not receive compensation for this.
- *Genetic Information Non-Discrimination Act (GINA)*: The genetic information obtained as a result of your participation in this research will not be included in your medical record. Information from which you may be personally identified will be maintained in a confidential, secure location at DUHS, accessible only by authorized members of the study team, and will not be disclosed to third parties except as described in this consent form, with your permission, or as may be required by law. The Genetic Information Nondiscrimination Act (GINA) is a Federal law that will protect you in the following ways:
    - Health insurance companies and group plans may not request genetic information from this research;
    - Health insurance companies and group plans may not use your genetic information when making decisions regarding your eligibility or premiums;
    - Employers with 15 or more employees may not use your genetic information when making a decision to hire, promote, or fire you or when setting the terms of your employment. GINA does not protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance. GINA also does not protect you against discrimination based on an already-diagnosed genetic condition or disease. It is possible that this study will

identify information about you that was previously unknown, such as disease status or risk. There are no plans to provide this information to you or your physician. There may be risks, discomforts, or side effects from being in this study that are not yet known.

Muscle biopsy

- You may experience some discomfort during the procedure and soreness after. The risks related to muscle biopsy of the leg are generally low (<1%). The most significant risks include an arterial bleed and local skin infection, both of which occur in well less than 1/1000 (0.1%). We will use sterile techniques to decrease these risks to you. We will also ask you to stop some blood thinners prior to the visit, if this is permitted by your doctor.

NIRS

- This is a non-invasive procedure and does not carry significant risks.

Muscle Ultrasound

- This is a non-invasive procedure and is less than minimal risk.

Reproductive Risks

- Pregnancy in women with heart failure is associated with an increased risk of complications for mothers and babies, including a significantly increased risk of maternal death. Women with heart failure are strongly advised to take steps to avoid an unplanned pregnancy, even if you do not participate in this study. In addition to the dangers to you, the effects of pregnancy on heart function would affect the interpretation of study results.
- There may be additional risks to a developing pregnancy from the study procedures, including the study drink. For these reasons, women who are pregnant, planning a pregnancy, or breastfeeding are not allowed to participate in this study.
- If you are a woman who could possibly become pregnant (you have not completed menopause, or you have not had a hysterectomy and/or both tubes and/or both ovaries removed) and you have a partner who could father children, a urine pregnancy test will be done at the first study visit and it must be negative in order to continue. If there is any chance you could have become pregnant between visits, additional tests may be done.
- Although study-related risks to a pregnancy are only a consideration during your visits, if you become pregnant during the study you will not be able to continue. If you think you are pregnant, you should notify the study doctor immediately. If pregnancy is confirmed, you will not continue in the study, but the study doctor will refer you to a specialist in high-risk pregnancy because of the dangers of pregnancy in women with heart failure. We will collect information

about the pregnancy and its outcome. We will do so via telephone call and if needed and you authorize us to do so, via medical chart review.

There may be risks, discomforts, drug interactions or side effects that are not yet known.

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?
You are unlikely to benefit from participating in this research study. However, your participation will help us understand how DeltaG affects the body's response to exercise. We hope that in the future the information learned from this study will benefit other people with your condition.

WILL MY INFORMATION BE KEPT CONFIDENTIAL?
Participation in research involves some loss of privacy. We will do our best to make sure that information about you is kept confidential, but we cannot guarantee total confidentiality. Your personal information may be viewed by individuals involved in this research and may be seen by people including those collaborating, funding, and regulating the study. We will share only the minimum necessary information in order to conduct the research. Your personal information may also be given out if required by law.

Your records may be reviewed in order to meet federal or state regulations. Reviewers may include representatives from the Food and Drug Administration, Office of Human Research Protections (OHRP), the Duke University Health System Institutional Review Board, Duke Office of Clinical Research, and others as appropriate. If any of these groups review your research record, they may also need to review your entire medical record.

Most tests done in research studies are only for research and have no clear meaning for health care. Some research results may be placed in your medical record (such as, but not limited to, basic laboratory testing and echocardiography results). However, if through testing we find out something that is clinically relevant to you, we will notify you regarding these results (for example, if you develop an abnormal heart rhythm during exercise that you do not have a history of having). We may also speak to your doctors.

The Department of Health and Human Services (HHS) has issued a Certificate of Confidentiality to further protect your privacy. With this Certificate, the investigators may not disclose research information that may identify you in any Federal, State, or local civil, criminal, administrative, legislative, or other proceedings, unless you have consented for this use. Research information protected by this Certificate cannot be disclosed to anyone else who is not connected with the research unless:

1) there is a law that requires disclosure (such as to report child abuse or communicable diseases but not for legal proceedings);

Duke University Health System

Consent to Participate in a Research Study
ADULT
Acute effects of ketones in heart failure

2) you have consented to the disclosure, including for your medical treatment; or

3) the research information is used for other scientific research, as allowed by federal regulations protecting research subjects.

Disclosure is required, however, for audit or program evaluation requested by the agency that is funding this project or for information that is required by the Food and Drug Administration (FDA).

You should understand that a Confidentiality Certificate does not prevent you or a member of your family 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. This means that you and your family must also actively protect your own privacy.

Finally, you should understand that the investigator is not prevented from taking steps, including reporting to authorities, to prevent serious harm to yourself or others.

The study results will be retained in your research record for at least six years after the study is completed. At that time either the research information not already in your medical record may be destroyed or information identifying you may be removed from such study results at DUHS. Any research information in your medical record will be kept indefinitely.

Some information collected in research studies is maintained in your medical record. However, for this study some information may be inaccessible until the end of the study, unless your physician(s) decide that it is necessary for your care.

If this information is disclosed to outside reviewers for audit purposes, it may be further disclosed by them and may not be covered by federal privacy regulations.

While the information and data resulting from this study may be presented at scientific meetings or published in a scientific journal, your name or other personal information will not be revealed. In addition, these data may be made publicly available but will not include any identifying information.

Some people or groups who receive your health information might not have to follow the same privacy rules. Once your information is shared outside of DUHS, we cannot guarantee that it will remain private. If you decide to share private information with anyone not involved in the study, the federal law designed to protect your health information privacy may no longer apply to the information you have shared. Other laws may or may not protect sharing of private health information.

Duke University Health System

Consent to Participate in a Research Study
ADULT
Acute effects of ketones in heart failure

WHAT ARE THE COSTS TO YOU?

You will not have to pay for any research procedures or tests that result from participating in this study.

You are still responsible for any deductibles or applicable co-pays for routine office visits, scans and blood work. Please talk to your doctor and study team about putting you in touch with a financial counselor to determine exactly what the deductible and co-pay will be for you; this is highly variable depending on your type of insurance.

WHAT ABOUT COMPENSATION?

You will be reimbursed up to $(405) for your expenses related to your participation (parking, gas, and time), which is described below.

You will receive financial compensation for your participation in this study. We will follow the following reimbursement scheme:

- Completion of Visit #1: $100 (with an extra $35 if you agree to participate in the muscle biopsy portion of the study given extra time needed)
- Completion of Visit #2: $100 (with an extra $35 if you agree to participate in the muscle biopsy portion of the study given extra time needed)
- Completion of Visit #3: $100 (with an extra $35 if you agree to participate in the muscle biopsy portion of the study given extra time needed)

The maximum total amount (if you complete all study visits) will be $405. You will be paid for each visit that you complete. Your reimbursement will be given to you as a Greenphire clincard at the completion of each visit.

Payment for participation in research is considered taxable income and Duke University is required in many cases to report this information to the Internal Revenue Service (IRS).

Duke University requires that you provide your name, mailing address, and social security number for this tax reporting purpose before payment can be issued. If you do not want to provide this information, you cannot be paid but you can still take part in the research study.

Research participant compensation made to a Duke University employee at any time during the calendar year will result in a 1099 (Miscellaneous Income) form being issued to the employee and a copy sent to the IRS regardless of the total amount paid.]

Duke University Health System

Consent to Participate in a Research Study
ADULT
Acute effects of ketones in heart failure

WHAT ABOUT RESEARCH RELATED INJURIES?
Immediate necessary medical care is available at Duke University Medical Center in the event that you are injured as a result of your participation in this research study. However, there is no commitment by Duke University, Duke University Health System, Inc., or your Duke physicians to provide monetary compensation or free medical care to you in the event of a study-related injury.

For questions about the study or research-related injury, contact Dr. Selvaraj at 919-684-8111 during regular business hours and at 724-679-8078 after hours and on weekends and holidays.

WHAT ABOUT MY RIGHTS TO DECLINE PARTICIPATION OR WITHDRAW FROM THE STUDY?

You may choose not to be in the study, or, if you agree to be in the study, you may withdraw from the study at any time. If you withdraw from the study, no new data about you will be collected for study purposes unless the data concern an adverse event (a bad effect) related to the study. If such an adverse event occurs, we may need to review your entire medical record. All data that have already been collected for study purposes, and any new information about an adverse event related to the study, will be sent to the study sponsor.

Your decision not to participate or to withdraw from the study will not involve any penalty or loss of benefits to which you are entitled, and will not affect your access to health care at Duke. If you do decide to withdraw, we ask that you email Dr. Selvaraj and let him know that you are withdrawing from the study. His email address is Senthil.Selvaraj@duke.edu.

We will tell you about new information that may affect your health, welfare, or willingness to stay in this study.

Your doctor may decide to take you off this study if your condition gets worse, if you have serious side effects, or if your study doctor determines that it is no longer in your best interest to continue. The sponsor or regulatory agencies may stop this study at anytime without your consent. Reasons why this might occur include is regulatory agencies believe that the study drug is associated with significant risks such as abnormal heart rhythms. If this occurs, you will be notified and your study doctor will discuss other options with you.

Your information and samples will be de-identified. De-identified means that all identifiers have been removed. The information and samples could be stored and shared for future research in this de-identified fashion. It would not be possible for future researchers to identify you as we would not share any identifiable information about you with future researchers. This can be done without again seeking your consent in the future, as permitted by law. The future use of your information and samples only applies to the information and samples collected on this study.

Duke University Health System

Consent to Participate in a Research Study
ADULT
Acute effects of ketones in heart failure

A description of this clinical trial will be available on https://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.

WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?
For questions about the study or a research-related injury, or if you have problems, concerns, questions or suggestions about the research, contact Dr. Selvaraj at 919-684-8111 during regular business hours and at 724-679-8078 after hours and on weekends and holidays.

For questions about your rights as a research participant, or to discuss problems, concerns or suggestions related to the research, or to obtain information or offer input about the research, contact the Duke University Health System Institutional Review Board (IRB) Office at (919) 668-5111.

Please initial whether you are also interested in the optional muscle biopsy:

_____Yes I agree to have the optional muscle biopsy

_____No I do not agree to have the optional muscle biopsy

OPTIONAL Blood samples for future research:
If you agree to have your blood samples taken for future research, they will be stored on Duke property with no identifying information that could link your sample to you on these specimens. We will use the amount of blood described in this consent form to store for future research purposes unrelated to the current purpose of the study. These samples will be maintained by Duke staff and processed by either a Duke or an external lab contracted through Duke. These samples will be kept indefinitely. Future researchers may have access to the data and blood samples, but no identifying information will be available to them or disclosed outside of DUHS.

Please initial next to the option you choose below.

_____Yes. I agree to have blood collected for future research.

_____No. I do not agree to have blood collected for future research.

Duke University Health System

Consent to Participate in a Research Study
ADULT
Acute effects of ketones in heart failure

STATEMENT OF CONSENT

"The purpose of this study, procedures to be followed, risks and benefits have been explained to me. I have been allowed to ask questions, and my questions have been answered to my satisfaction. I have been told whom to contact if I have questions, to discuss problems, concerns, or suggestions related to the research, or to obtain information or offer input about the research. I have read this consent form and agree to be in this study, with the understanding that I may withdraw at any time. I have been told that I will be given a signed and dated copy of this consent form."

Signature of Subject	Date	Time
Signature of Person Obtaining Consent	Date	Time