UNIVERSITY OF PENNSYLVANIA RESEARCH SUBJECT COMBINED INFORMED CONSENT AND HIPAA AUTHORIZATION FORM

Protocol Title:	The Effect of KNO_3 Compared to KCl on Oxygen Uptake in Heart Failure with Preserved Ejection Fraction (KNO_3CK OUT HFPEF)
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Why am I being asked to volunteer?

You are being invited to participate in a research study because you have a diagnosis of heart failure with preserved ejection fraction (HFpEF). This is a condition that causes patients to be short of breath and limited in what they can do in their daily lives. Currently, there are no approved drugs for this condition. We are trying to find new therapies for this condition. Our goal is to look at the effects of Potassium Nitrate, a dietary supplement, on your condition. Your participation is voluntary which means you can choose whether or not you want to participate. If you choose not to participate, there will be no loss of benefits to which you are otherwise entitled. Before you can make your decision, you will need to know what the study is about, the possible risks and benefits of being in this study, and what you will have to do in this study. The research team is going to talk to you about the research study, and they will give you this consent form to read. You may also decide to discuss it with your family, friends, or family doctor. You may find some of the medical language difficult to understand. Please ask the study doctor and/or the research team about this form. If you decide to participate, you will be asked to sign this form.

What is the purpose of this research study?

The purpose of this study is to test whether Potassium Nitrate (KNO_3) will improve exercise in people with HFpEF. In HFpEF, 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 HFpEF also have problems with their arteries and muscles that affect their ability to exercise. Potassium Nitrate has been shown to improve how muscles work and also improve blood flow to working muscles in the body in healthy individuals. We previously conducted a pilot study with our KNO_3 pills, and they appear to be safe in subjects with HFpEF. We would like to now study these pills in a larger group of patients to see if we can improve exercise in HFpEF.

The use of Potassium Nitrate in this study is experimental. Potassium Nitrate has not been approved by the Food and Drug Administration (FDA) for the use being evaluated in this study.

How long will I be in the study? How many other people will be in the study?

You will be involved with this study for approximately 3.5 months (14 weeks). The study involves 3 visits to our research center. The details of the visits are outlined below. We will enroll approximately 84 individuals in this study.

If you are being enrolled at the CMCVAMC or the University of Pennsylvania, you are also eligible to participate in a cardiac magnetic resonance imaging (MRI) sub-study that involves 2 additional visits. If you choose to participate in this sub study, a cardiac MRI study will be performed during each of these 2 visits, at the Corporal Michael J. Crescenz VA Medical Center (CMCVAMC) or the Hospital of the University of Pennsylvania. You can choose to participate in the main study with or without participation in the cardiac MRI sub-study.

What am I being asked to do?

If you participate in this study, you will be asked to come to the research center for a total of 3 visits. On each day, you will be asked to perform several tests related to exercise, heart function, and muscle function, which will be discussed below. During the first visit, we will perform tests to make sure you fit the criteria for our study. We will then ask you to start study medications for approximately 6 weeks ***(Intervention Phase 1)***. At the end of that approximate 6 weeks, we will ask that you come back to our research center for testing, including an exercise test. After this visit, you will not take any study medications for 1 week to allow the drugs to wash out of your system ***(Washout Period)***. We will then start you on a second study medication ***(Intervention Phase 2)*** for another approximate 6 weeks. At the end of this second approximate 6 week period, you will be asked to come in and repeat

the tests for a 3rd and final time, which will include your final exercise test. Your participation in the study will be over at the end of this 3rd visit.

This study is a crossover study, which means that all participants will receive the "active" study medication, KNO_3, for approximately 6 weeks, and all participants will also receive "Placebo," which is a study medication that has no known actions on your body. The placebo that we will use will be potassium chloride (KCl). Neither you, nor the study investigators, will know which drug you are getting at which time. However, we can always get this information from the research pharmacy if we need to for an emergency.

If at any point, you are experiencing intolerable side effects, or your blood tests indicate that it will not be safe, we will ask you to stop the study medication, and your participation in the study will be over. You can also request to leave the study at any time. During the course of the study, we may need to contact you regarding study related issues.

Procedures and Visit Schedule

Prior to Visit 1 – a member of our research team may contact you to discuss foods that we would like you to avoid during the study.

Visit 1: *In person visit at our research center. This visit will take one-half of a day.*

On the first day, we will perform tests and studies to make sure you are a good candidate for our study (as discussed below). At the end of this visit, if you are eligible, you will be randomized to study medications for the initial 6-week period ***(Intervention Phase 1)***.

During this visit, we will have you speak with a member of our research team to learn about what foods we would like you stay away from during this study (foods high in inorganic nitrate). We will also give you a questionnaire about your heart failure symptoms. We will also perform a physical exam, and obtain blood, urine and saliva (spit) samples from you.

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

- *Review and sign this informed consent form.*
- *Vital Signs and brief Physical Exam* - We will check your blood pressure and heart rate, and a qualified member of our staff will perform a brief physical exam.
- *Blood Draw* - We will draw blood from you. Blood will be drawn by inserting an intravenous catheter ("an IV") into a vein in your arm. We will measure various substances in the blood that tell us about the pressures in your heart, your nitrate levels, and your methemoglobin levels. We will discuss methemoglobin more below, but in brief, this is a compound that can accumulate in the blood and make it more difficult for your blood to carry oxygen to the body. Some drugs, and possibly potassium nitrate, may increase your methemoglobin levels, so we want to track this carefully. We will draw ~4 tablespoons of blood during the blood draw. We will also collect saliva (spit) and urine samples.

- *Questionnaires* - a member of our research team will speak to you about foods that we would like you to avoid during this study. We will also give you a questionnaire that asks you questions about your symptoms and how you feel you are functioning in your day-to-day life (Kansas City Cardiomyopathy Questionnaire).
- *Cognitive Assessment* - a member of our research team will administer a battery of cognitive tests (tests of some aspects of brain function). This testing will take approximately 30 minutes and is performed with a computer. Your responses are then uploaded to an internet third-party server that calculates a score that quantifies your cognitive function. Your personal identifiable information (such as name, date of birth, social security number or medical record number) is not uploaded to the server. Therefore, the server will have no way of linking your responses to your identity.
- *Arterial Tonometry* - This is a simple non-invasive test in which we will examine the pressure in your blood vessels. 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 your wrist, over the side of your neck, and finally in your groin to measure the pulse.
- *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. This takes approximately 20 minutes.
- *Electrocardiogram* - During this procedure, we will place electrodes (stickers) on your chest to capture the electrical signals from the heart.
- *6 minute walk test* - You will be asked to do a six-minute walking test. The object of this test is to walk as quickly as you can for six minutes in a hallway track (up and down the corridor) so that you cover as much ground as possible. You may slow down if necessary. If you stop, we ask that you to continue to walk again as soon as possible. You will be kept informed of the time and you will be encouraged to do your best. Your goal is to walk as far as possible in six minutes. We do this test because we want to make sure that your oxygen levels do not drop too much during exercise, which would make you ineligible to continue in the study.
- *Activity Monitor* - This device will track the number of steps you take in a day and how active you are. We would like you to wear this device during the last week of each intervention phase. This device is similar to the size of a watch and is worn on your wrist. We will ask you to return the device to the research team when you return for your following visit. The device is not waterproof, so you will need temporarily to take it off to take baths or showers.

- *Pulse wave analysis watch* - You will be asked to wear a watch that takes the pulse at your wrist continuously. We will ask that you try to wear the watch during the last week of each intervention phase. We will also ask you to wear the watch during your exercise studies in our research facility. We will teach you how to use the watch and you will receive written instructions about its use. The watch is not waterproof, so you will need temporarily to take it off to take baths or showers. You will be asked to return the device to our research team.
- *Randomization* - After baseline testing is complete and your eligibility is verified, you will be randomly assigned to receive either potassium nitrate or placebo first. You will not be told which medication you are getting. Investigators will not know which medication you are getting, but we can find out if needed, in the case of an emergency.

You will then be asked to start study medications to be taken **twice daily** during.

Intervention Phase 1:
~1 week phone call: We will call you approximately 1 week after starting study medications to see how you are doing and to discuss foods that we would like you to avoid during the study. If you are feeling well, we will then increase the dose to **three times a day. The medication can be taken with food.** If you are having side effects, we may ask you to come into our research center for us to see you. If you are on certain medications, such as potassium-sparing diuretics (water pills) and have impaired kidney function, we may also check your blood after about a week on the increased dose of study medication to make sure your electrolytes are okay. We will ask you to take study medications for approximately 6 weeks.

Visit 2: *This visit will occur approximately 6 weeks after your first visit. Please plan on this visit to last from 8 am – 5 pm.*
Please arrive in the morning before taking your morning dose of study medication and before you have eaten. We will place an IV in your arm and check the levels in your blood. We will also be collecting RNA (ribonucleic acid) from your blood. RNA is a genetic material that has a major role in making proteins. Proteins are the building blocks of your body, cells, and organs. We are interested to see how the study medication affects your RNA, and if your RNA might predict your body's response to the study medication. We will also collect another saliva and urine sample. We will then give you a light breakfast with your morning dose of study medication. We will then ask you about side effects and a study team member will talk to you about your diet again. We will also perform cognitive assessment that will test some aspects of your brain function for 30 minutes. About two hours after you have taken the study medication, we will check your blood levels from your IV and collect another spit and urine sample. We will then ask you to perform the study procedures again, as listed below.

List of Visit #2 Procedures:

- *Vital signs*
- *Light breakfast with study medication*
- *Questionnaires* – In addition to discussing your diet with a member of our research team, we will also ask you about any potential side effects you may be experiencing from the study medication. We will also administer the questionnaire asking about your heart failure symptoms (Kansas City Cardiomyopathy Questionnaire).
- *Blood draws from IV and saliva and urine samples*
- *Cognitive assessment*
- *Arterial tonometry*
- *Doppler echocardiogram*
- *Bicycle Exercise Test (see below next) with peak exercise blood sample*
- *Muscle MRI with leg exercise*

Bicycle Exercise Test – We will ask you to perform a bicycle exercise test where you will be lying on your back. This test will be used to assess your overall exercise capacity. The test will begin with a low level of resistance that will then increase every 3 minutes. We would like you to exercise for as long as you possibly can, as the goal is to push yourself to your peak. We will be monitoring you throughout this period and will stop you if we see anything unsafe. When you stop exercising, we will ask you to remain lying in the same position for about 6 minutes while we continue to collect information about your recovery. The total length of this bicycle exercise test will depend on you.

During bicycle exercise testing you will breathe through a mouthpiece that is connected to a machine that monitors the air that you breathe in and out. Specifically, the machine tells us about how much oxygen you are using, and how much carbon dioxide your body is making during exercise. We will also continuously monitor your heart rate and rhythm, and we will be checking your blood pressure frequently during the study. We will also monitor the oxygen levels in your blood using a finger probe. This information will allow us to determine how much oxygen your body is using during exercise, the electrical conduction of your heart, how fast your heart is beating during exercise, and how much pressure there is in your arteries during exercise. When available, we will also place a special device over your calf and forearm muscle. These devices, called Near-Infrared Spectroscopy devices, or NIRS in short, use light to measure the amount of oxygen in your muscles. The device is smaller than an iPhone and rests on your skin. There is no pain or discomfort associated with this and you do not feel the device measuring the levels.

Additionally, we will assess how much blood your heart is pumping (cardiac output) during this exercise test. This will be done at several points during the study (for example, before exercise, during exercise, and during recovery). We will assess cardiac output using our echo machine to take pictures of the heart and its blood flow during exercise. We may also take pulse recordings of your wrist and neck. We will ask you to wear the pulse recording watch during the exercise test. The length of the exercise test will

vary based on how long you can exercise for, but we want you to exercise for as long as you safely can while we monitor you the entire time. We will draw a blood sample from your IV immediately when you stop exercising.

MRI of your calf muscles – There is evidence that patients with heart failure have problems in their muscles that makes them get tired quickly. A main goal of this study is to look at this problem and assess how the skeletal muscles use oxygen. This process occurs within the mitochondria on your skeletal muscle, where energy is produced. Problems with the mitochondria have been reported in some, though not all, studies of patients with heart failure. We will be assessing your mitochondria and skeletal muscle function using MRI with exercise performed in the MRI scanner. This focuses on skeletal muscle mitochondria function in the calf muscles and also looks at blood flow to the exercising muscles. This test will take about 2 hours, though you will spend less than 1.5 hours in the MRI scanner. We will ask you to perform leg exercise in the scanner while the MRI machine measures how the muscles and blood flow respond and recover from this exercise. Importantly, we do not want the MRI measurements to be influenced by your bike exercise, so we will make sure you do the MRI either before, or 3 hours after, your bike test, depending on availability of the MRI scanner, the research center, and your schedule. Depending on scheduling, and your availability, the MRI test may be performed on a different day than the exercise test.

Cardiac MRI Sub-study (optional): If you were enrolled in the main study either at the University of Pennsylvania or at CMCVAMC you may also be approached about taking part in a sub-study. If you agree to participate in this sub-study you will undergo one additional test (cardiac MRI with regadenoson administration) twice, in addition to the tests already involved in the main study. A cardiac MRI with regadenoson is a stress test of your heart that is performed using an MRI machine. This test is a stress test of your heart using medications and is like a nuclear stress test. There is evidence that patients with heart failure have problems with the blood flow to their heart muscle that may cause them to get tired quickly. A main goal of the sub-study is to measure the blood flow to your heart muscle after giving a stress medication (regadenoson) through an IV line. This medication increases the blood flow in the arteries supplying your heart muscle. We can measure the blood flow to your heart using the MRI machine. We will also measure the blood flow in your heart muscle after the effects of the stress medication are no longer present. This will give us an understanding as to the function of the blood vessels that supply blood to your heart muscle. For this test, we will first check an electrocardiogram (ECG) of your heart MRI. This involves placing patches on your chest, arm and leg which record the electrical activity of your heart. After this we will place an IV in your arm. We will then proceed with the MRI scan, which will take 45-50 min. During this time, you will be asked to hold your breath on and off for 1-15 seconds while pictures of your heart are being taken. During the test, a physician involved with the study will come in and give you the medication (regadenoson) through the IV. We will then give you the IV dye (gadolinium) that is used to look at blood flow in your heart muscle. We will then take pictures of your heart to measure how much blood flow there is in

your heart muscle. Once this is done a physician will come in and give you a second medication (IV aminophylline) which is used to reverse the effects of the first medication. Following this we will take more pictures of your heart including pictures that look at the blood flow in your heart muscle and if there is scarring in your heart. The cardiac MRI test may be performed on a different day than the exercise test or the MRI scan of your legs (~ 1 week prior to or after). The same test will be performed around the time of Visit 3.

Criteria that will prompt discontinuation at the 6 - week visit: Some events during the first 6 weeks of treatment with the study medication may prompt discontinuation from the study. These include the development of new symptoms that may require further evaluation and/or changes in your medication regimen. In some instances, we may ask that you return for an extra visit to make sure that your blood pressure and your blood work are within safe limits.

***1 - week washout period*:** Following the completion of the studies during your second visit, we will ask that stop taking any of our study medication for 1 week, to allow the drug to clear out of your body. You should continue all of your other regularly-prescribed medications.

***Intervention Phase 2*:** At the end of the washout period, we will give you the second study medication to be taken **twice a day**. This will be either KNO_3 or Placebo, and will be the opposite of what you got during Intervention Phase 1. In this way, every subject in the study will receive both KNO_3 and Placebo, though the subjects may receive these medications in a different order.

~1 week phone call: We will call you after about one week of taking the **Intervention Phase 2** study medications twice a day. We will discuss how you are feeling, what foods we would like you to avoid, and any side effects. If you are having side-effects, we may ask you to come in to our research center to be evaluated. If you are doing well, we will increase the dose of the **Intervention Phase 2 study medications to three times a day with a meal.**

Visit 3: *This visit will occur after you have been on Intervention Phase 2 study medications for approximately 6 weeks. Please plan on this visit to last from 8 am – 5 pm.*

Please arrive in the morning before taking your morning dose of study medication and before you have eaten. We will place an IV in your arm and check the levels in your blood. We will also be collecting RNA (ribonucleic acid) from your blood. RNA is a genetic material that has a major role in making proteins. Proteins are the building blocks of your body, cells, and organs. We are interested to see how the study medication affects your RNA, and if your RNA might predict your body's response to the study medication. We will also collect another saliva and urine sample. We will then give you a light breakfast with your morning dose of study medication. We will then ask you about side effects and a study team member will talk to you about your diet again. We will also perform cognitive assessment that will test some

aspects of your brain function for 30 minutes. About two hours after you have taken the study medication, we will check your blood levels from your IV and collect another urine and spit sample. We will then ask you to perform the study procedures again, as listed below.

List of Visit #3 Procedures: This visit will be exactly the same as Visit #2

- *Vital signs*
- *Light breakfast with study medication*
- *Questionnaires* – In addition to the discussing your diet with a member of our research team, we will also ask you about any potential side effects you may be experiencing from the study medication. We will also administer the questionnaire asking about your heart failure symptoms (Kansas City Cardiomyopathy Questionnaire).
- *Blood draws from IV, urine, and saliva samples*
- *Cognitive assessment*
- *Arterial tonometry*
- *Doppler echocardiogram*
- *Bicycle Exercise Test with blood sample at peak exercise*
- *Muscle MRI with leg exercise (may be performed on a separate day)*

***Your participation is complete after Visit 3*. We will compare your results from Visit 2 and Visit 3.**

Also, if you are taking part of the cardiac MRI sub-study, you will undergo a MRI study of your heart similar to the one performed prior to Visit 2. The cardiac MRI test may be performed on a different day than (~ 1 week prior to or after) Visit 3.

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

Visit 1	• Read and sign this informed consent form (**ICF**). • If you are a pre-menopausal woman, we will **confirm that you are not pregnant** using a urine pregnancy test. • Brief **physical exam,** and record **vital signs**. • Speak with one of our team members to discuss eating habits. • Complete a **questionnaire on your heart failure symptoms**. • Have your **blood drawn and give a saliva and urine sample**. • **Cognitive assessment** • The **arterial tonometry** test.

	• Have a **doppler echocardiogram** • **Have a 6-minute walk test**. **If you meet all of our criteria:** • **You will be asked to start study medications (*Intervention Phase 1).*** • **Approximately 5 weeks into interventional Phase 1, the Aurora and Actigraph devices will be given to you. The goal will be for you to wear these devices during the final week of interventional Phase 1 to look for differences with each therapy. We will ask you to bring back the devices at your next visit (Visit 2).**

Visit 2 (after ~6 weeks of study medications)	• Record **vital signs and perform a pill count**. • Retrieve the **activity monitor** and the **pulse wave analysis watch** to download the data. • Have your **blood drawn and a new IV placed**. • **Give a saliva and urine sample**. • If you are a pre-menopausal woman, we will **confirm that you are not pregnant** using a urine pregnancy test. • Have a light breakfast with your morning dose of study medication. • Speak with a member of our research team about your recent eating habits. • Complete a **questionnaire on your heart failure symptoms**. • **Cognitive assessment** • Discuss **potential side effects** *~ After approximately 2 hours~* • Blood draw from your IV and give a saliva and urine sample. • The **arterial tonometry** test. • Have a **doppler echocardiogram.** • Complete the **Bike Exercise Tests with blood sample at peak exercise**.

	• Complete the **MRI of your calf (may be performed during a separate visit)**. ***After all Visit 2 assessments are complete, you will start the 1-week washout period during which you will NOT take any study medication.*** ***Please continue your other medications.*** • ***After this 1 week washout period, you will start Intervention Phase 2 study medications.*** • **Approximately 5 weeks into interventional phase 2, the Aurora and Actigraph devices will be given to you. The goal will be for you to wear these devices during the final week of interventional Phase 2 to look for differences with each therapy. We will ask you to bring back the devices at your next visit (Visit 3).**
Visit 3 (after ~6 weeks of Intervention Phase 2 study medications)	• Record **vital signs and perform a pill count**. • Have your **blood drawn and an IV placed**. • **Give a saliva and urine sample**. • If you are a pre-menopausal woman, we will **confirm that you are not pregnant** using a urine pregnancy test. • Have a light breakfast with your morning dose of study medication. • Speak with a study team member about your eating habits. • Complete a **questionnaire on your heart failure symptoms**. • **Cognitive assessment** • Discuss **potential side effects**. *~ After approximately 2 hours~* • Blood draw from your IV and give a saliva and urine sample. • The **arterial tonometry** test. • Have a **doppler echocardiogram.** • Complete the **bike exercise tests with blood draw at peak exercise**. • Complete the **MRI of your calf**. • Return your activity monitor and pulse wave analysis watch. ***Your participation in the study is now over.***

What are the possible risks or discomforts?

Study Drug - Potassium nitrate (KNO_3)

Currently, we do not have much information regarding possible side effects of Potassium Nitrate in patients with HFpEF. In other studies of generally healthy individuals, nitrate given either as a juice or in capsule form was generally well tolerated. If taken without food, the most common side effect people experienced was stomach discomfort. This was prevented by taking the study drug with a meal. Other possible side effects include:

- Slight headache
- Dizziness
- Lightheadedness
- Low blood pressure
- Stomach ache, diarrhea, nausea, or vomiting
- Shortness of breath
- Flushing
- Rash
- Changes in blood pressure when standing up
- Orthostatic hypotension - This is a large change in blood pressure that occurs from moving from sitting to standing and can cause people to get very light headed and even pass out.
- Methemoglobinemia - One of the main functions of blood is to carry oxygen from the lungs to the rest of the body. This is accomplished by something called “hemoglobin” that is found in blood. Hemoglobin exists in many forms, one of which is methemoglobin. This version is not active and cannot participate in carrying oxygen. In healthy individuals, methemoglobin makes up less than 3% of circulating hemoglobin. Some genetic conditions, and certain drugs, can increase methemoglobin levels. Nitrates, and drugs in this family, are in this group. In our preliminary studies, we found that potassium nitrate does not significantly increase the levels of methemoglobin. However, we will measure your methemoglobin levels during this study and if you are a male of African, Asian, or Mediterranean decent, we will make sure that you don’t have Glucose- 6-phosphate dehydrogenase (G6PD) deficiency prior to starting study medications, as this could make you more susceptible to methemoglobinemia.

We did not see any serious side effects from potassium nitrate in our pilot study. If you experience any side effects you find too uncomfortable, you may withdraw from the study at any time. The study team will specifically assess you for the presence of symptoms after the medication is initiated or after the dose in increased, in order to determine whether it is safe for you to continue taking these medications.

Potential Drug Interactions and Instructions during the Study

There is not much information on potassium nitrate in subjects with heart failure. You are not eligible for this study if you are on other nitrate-containing medications such as isosorbide mononitrate (Imdur) or isosorbide dinitrate (Isordil).

If you take medications for erectile dysfunction, such as sildenafil (Viagra), tadalafil (Cialis), or vardenafil (Levitra) we will ask you to stop taking this medication for 7 days before starting the study and for 7 days after study completion. This is due to a chance that taking both nitrates and these medications could lead to a dangerous drop in your blood pressure.

Potassium nitrate (KNO_3) and Potassium chloride (KCl) contains potassium, which can be dangerous at high levels. We will monitor your potassium level at each study visit to minimize the chance of harm.

A major source of nitrates is your diet. Our team member(s) will meet with you several times during the study to discuss your diet and what foods to avoid during the study.

Finally, we will ask **you to not use mouthwash during the study**. While brushing your teeth and flossing are fine, mouthwash kills the bacteria in your mouth. These bacteria are needed for activation of the study medication. Please let us know if you are put on antibiotics during the study.

Drug Interaction and Instructions Summary

- You are not eligible for this study if you take any form of nitrates (nitroglycerin, isosorbide mononitrate, isosorbide dinitrate).
- You must not take medications for erectile dysfunction, such as sildenafil (Viagra), tadalafil (Cialis), or vardenafil (Levitra) for 7 days before starting the study and for 7 days after the study is complete. This is to avoid any a dangerous drop in your blood pressure.
- Do not use mouthwash during the study.
- Our study team member(s) will give you information regarding which foods to avoid during the study.
- Please let us know if you are started on antibiotics for any reason during the study.

Possible Risks or Discomforts of Study Procedures

Arterial Tonometry

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

Doppler Echocardiogram

- 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.

Bicycle Exercise Test

- Pushing yourself hard during the exercise test may make you uncomfortable. It is expected that you will become tired and short of breath, and that your blood pressure, heart rate, and other vital signs will change as a result of exercise. We ask that you push yourself, and do the most that you can possibly do. You may feel nauseous, light headed, or develop aches and pains as a result of the exercise study and pushing yourself hard.
- This exercise testing protocol is considered safe. Rarely, people have an adverse event during exercise. The risk of this happening is the same in our lab as it would be if you exerted yourself elsewhere. You will be closely monitored throughout the entire period by individuals who are trained to respond to situations that might develop.
- You will likely become short of breath and tired during this test. This test may result in exhaustion or abnormal heart rates, however you will be monitored using EKGs to check for this. We will also closely monitor your blood pressure, heart rate, and oxygen levels. In rare cases, exercise may lead to a major heart complication (such as a heart attack, passing out, or death). We will have staff on hand to monitor you throughout the process and will be equipped to handle emergencies in the event of any problems.
- Importantly, exercise testing has been shown to be safe in the vast majority of stable patients with heart failure.

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 of the vein. These problems generally resolve over time on their own after the IV has been removed.
- Blood samples collected during testing will be stored confidentially in dedicated blood laboratory space. Your blood samples will be analyzed for research purposes. All collected blood samples will be stored with your unique coded identifier and only approved study personal will have access to the key to the code.

MRI Risks:

- **Flying Objects:** The known risks associated with this study are minimal. Implanted medical devices and metallic foreign fragments inside your body may pose a risk if you were to enter the MRI magnet room. Therefore, questions regarding medical and work history will be asked prior to your exam. The greatest risk is a magnetic object flying through the air toward the magnet and hitting you. To reduce this risk we require that all people involved with the study remove all magnetic metal from their clothing and all magnetic metal objects from their

pockets. No magnetic metal objects are allowed to be brought into the magnet room at any time except by approved personnel. In addition, once you are in the magnet, the door to the room will be closed so that no one inadvertently walks into the room.

- **Magnetic Fields Health Risks Statement:** There is no known health risk associated with exposure to magnetic fields during an MRI. There are minimal risks from the loud noise associated with the MRI scanner and from the discomfort of lying on a hard surface. We shall provide you with protective earplugs as necessary and make every attempt to ensure your comfort with blankets, etc. during your time in the scanner.

- **Pregnancy:** Although there are no known risks related to MRI on pregnant women or a fetus, there is a possibility of yet undiscovered pregnancy related risks. Since there is no possible benefit from participating in this protocol for a pregnant woman, we will exclude pregnant women. A negative urine pregnancy test will be required before a woman of child-bearing potential can participate in this study. If you are post-menopausal for at least one year, or have had your ovaries removed, you will not be required to undergo a urine pregnancy test prior to obtaining your MRI scan.

- **Metallic Foreign Bodies Statement:** Implanted medical devices and metallic foreign fragments inside your body may pose a risk if you were to enter the MRI magnet room. Devices such as Pacemakers, Internal Cardiac Defibrillators, Insulin Pumps, and other medical devices may also prevent you from safely having the MRI. Therefore, questions regarding medical and work history will be asked prior to your exam by the MRI technician. If any of the above pertain to you, we may need to investigate further to make sure that the MRI will be safe for you to have. This may include performing an X-ray or obtaining old X-ray results. We may also discuss your situation with our radiologist(s) and MRI technicians to make sure you will be safe.

The MRI performed under this protocol is not for medical purposes, and the images are not planned to be interpreted by a physician.

- **Incidental Findings Clause:** This MRI is not a clinical scan. It is possible that during the course of the research study, the research staff may notice an unexpected finding(s). Should this occur, the finding(s) will be considered by the appropriate personnel and the PI will inform you if necessary. These possible finding(s) may or may not be significant and may lead to anxiety about your condition and to further work-up by your physician.

- **Experimental Device Clause:** Some aspects and attachments of the MRI study are not FDA approved but are considered to pose no more than minimal risk.

- **MRI 7T Clause:** While the FDA has not approved the use of 7.0T (this number reflects the strength of the magnetic field generated) MRI scanners for diagnostic use, it does consider magnetic field strengths up to 8.0T to pose no more than minimal risk. No persistent adverse effects have been reported by facilities with magnetic field strengths at 7.0T. However, some people have reported transient dizziness, nausea, or a metallic taste upon being moved into and out of the scanner. These effects typically last less than 10 minutes, and can be minimized by reducing the speed at which the person is moved inside the magnet. If the 7T MRI Scanner is not available, we may use a different MRI scanner that operates at a lower magnet strength of 3T. We will use the same safety precautions, regardless of the magnet strength to maximize safety.
- This research study may involve exposure to radiation if an X-ray is needed prior to your MRI scan. Therefore, you may receive a radiation dose. This radiation dose would not be necessary for your medical care and would occur only as a result of your participation in the study. At doses much higher than you would receive, radiation is known to increase the risk of developing cancer after many years. At the doses you would receive, it is very likely that you would see no effects at all.
- If you are not a good candidate for undergoing MRI studies due to contraindications or safety concerns, but you are otherwise a good candidate for the study, you may be enrolled in the study. In this case, you will undergo all study procedures except the MRI studies.
- Recent studies have shown that traces of gadolinium may remain in the body long-term after contrast administration. This risk increases with the number of administrations, but reviews to date have not identified adverse health effects from gadolinium retained in the brain or bodily tissues after MRI ([Gadolinium agents administered in this study are thought to minimize or eliminate this risk]). If you would like more information, please go to this link https://www.fda.gov/Drugs/DrugSafety/ucm589213.htm or ask the study team for more information.

Reproductive Risks

Because of the effects of this drug, there could be serious harm to unborn children or children who are breast-feeding. These effects could also harm the mother. It is also possible that harmful side effects that are not yet known could happen to both the mother and unborn or breast-feeding child. If you are currently pregnant, it is important that you inform the investigator because you will not be able participate in the study. If you are able to become pregnant, you will be given a pregnancy test before entry into the study. You will be

asked to use a medically accepted method of birth control (such as an IUD, birth control combination pill, patch, or ring, progestin-only pills, Depo Provera Shot, Implanon, complete abstinence, or condoms) while you participate in the study. You should not become pregnant while you are in this study. If you do become pregnant, you must tell the study investigator and consult an obstetrician or maternal-fetal specialist. If you become pregnant during this study, 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.

Risks of Genetic Testing

This research includes genetic testing. Even without your name or other identifiers, your genetic information is unique to you. The researchers believe the chance that someone will identify you is very small, but the risk may change in the future as people come up with new ways of tracing information.

There can be a risk in knowing genetic information. New health information about inherited traits that might affect you or your blood relatives could be found during a research study. Even though your genes are unique, you share some of the same genes with your blood relatives. Although we are not able to know all of the risks from taking part in research on inherited traits, we believe that the risks to you and your family are very low, because your samples will be coded. Research results will not be returned to you or your doctor.

Very rarely health or genetic information could be misused by employers, insurance companies, and others. For example, it could make it harder for you to get or keep a job or insurance, or life insurance companies may charge a higher rate based on this information. We believe the chance these things will happen is very small, but we cannot make guarantees.

A federal law (Genetic Information Non-Discrimination Act, GINA) helps reduce the risk from health insurance or employment discrimination. The law does not include other types of misuse by life insurance or long term care insurance. If you want to learn more about GINA, you can find information about it on the internet or ask the study staff.

Cardiac MRI Risks: The risks involved with having an MRI scan are similar to the general MRI risks mentioned above. In addition during the cardiac MRI you will receive gadolinium and regadenoson.

- **Gadolinium:** Gadolinium is a dye that is given through the IV line to look at the blood flow in your heart muscle. It is used as part of regular testing during MRI scans of the heart and other organs in the body to look for disease. Adverse reactions to gadolinium include injection site pain (from the needle), burning at injection site (if the dye contacts the skin), headache, dizziness or faintness, a decrease in your blood pressure, nausea, vomiting, sweating and paresthesias. Rarely, a severe allergic

reaction can occur with use of the contrast agent including: rash, hives, or urticaria. Very rarely there may be bronchospasm (similar to an asthma attack). Severe, life-threatening reactions are very rare (0.001% to 0.01%). Fatal reactions to gadolinium occur but are extremely rare. Gadolinium that is administered to patients with acute kidney failure or severe kidney disease can result in nephrogenic systemic fibrosis (NSF), a rare and serious syndrome that involves fibrosis of skin, joints, eyes, and internal organs. Patients with acute kidney failure or severe chronic kidney disease cannot be included into this study and subjects, whose kidney function has deteriorated below a certain level (glomerular filtration rate less than 40 mL/min) while in the study, will not receive gadolinium for the MRI scan even if they were originally enrolled in the cardiac MRI sub-study.

Recent studies have shown that traces of gadolinium may remain in the body long-term after contrast administration. This risk increases with the number of administrations, but reviews to date have not identified adverse health effects from gadolinium retained in the brain or bodily tissues after MRI ([Gadolinium agents administered in this study are thought to minimize or eliminate this risk]). If you would like more information, please go to this link https://www.fda.gov/Drugs/DrugSafety/ucm589213.htm or ask the study team for more information.

- **Regadenoson:** Regadenoson is a medication given during the MRI scan which increases the blood flow to the muscle of the heart. Common side effects of regadenoson include headache, dizziness, nausea, abdominal discomfort, chest discomfort, flushing, and shortness of breath. These resolve after the effect of the medication wears off. We will check an ECG before you have the test done to make sure that it is safe to give you this medication. We will also have a heart specialist doctor near the scanner at the time you are receiving this medication to ensure your safety. You can also talk to the technologist over the intercom in the MRI scanner if you have any symptoms during the stress test. Once we have taken pictures of the blood flow in your heart muscle after giving regadenoson, we will give you a medication through the IV (aminophylline) that reverses the effects of the regadenoson.

Other Risks

Although a breach in confidentiality is a potential risk, we have implemented various measures to minimize the possibility of a breach in confidentiality. If you decide to participate in the study, you will be assigned a unique identifier number (example: '#023') and all your data entered into our database will be linked to this identifier and not to your name or other personal information.

If you are injured while participating in this study, you should inform your primary care physician that you are participating in this research study. Your primary care physician can also contact us regarding your participation in this study at any time.

In addition to the possible risks detailed above, the research may involve risks that are currently unforeseeable.

This is not a complete list of possible side effects, but the most significant are listed above. If you notice other effects or new symptoms not listed above, please contact the study team. You can contact Dr. Payman Zamani at 267-496-5380.

What if new information becomes available about the study?

During the course of this study, we may find more information that could be important to you. This includes information that, once learned, might cause you to change your mind about being in the study. We will notify you as soon as possible if such information becomes available.

What are the possible benefits of the study?

You may not benefit from participating in this research study. However, your participation will help us understand how Potassium Nitrate affects the body's response to exercise.

What other choices do I have if I do not participate?

There is no penalty if you choose not to join the research study.

What other choices do I have if I do not participate?

There is no penalty if you choose not to join the research study.

At this moment, we don't have effective treatments for your condition; however, we don't yet know whether the therapy we are testing in this study is effective.

As an alternative to participation, you may continue your standard care and therapy without joining the research study. You may also discuss alternate forms of therapy with your personal physician.

Will I be paid for being in this study?

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

- Completion of Visit #1: $150
- Completion of Visit #2: $250
- Completion of Visit #3: $250

The maximum total amount (if you complete all study visits) will be $650. You will be paid for each visit that you complete. If you meet a pre-specified time of wearing the pulse analysis watch (70% of the monitoring period), you will be compensated with an additional $100.

If you participate in the cardiac MRI sub-study, you will also receive the following compensation:

- Completion of Visit #2 Stress MRI visit: $125
- Completion of Visit #3 Stress MRI visit: $125

Compensation will be in the form of a check from the University of Pennsylvania or prepaid card (GreenPhire ClinCard). If it's in the form of a check it will be mailed out approximately 4-8 weeks after each visit is completed. If it's in the form of prepaid card you will receive it after completion of your visit or when your eligibility for payment is analyzed (Aurora payment).

Please note: In order to be compensated for your participation in this study, you must provide your Social Security Number. Additionally, please note that the University of Pennsylvania is required to report to the IRS any cumulative payments for participation in research studies that exceed a total of $600 in a calendar year.

Will I have to pay for anything?

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 not related to this study. 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 happens if I am injured from being in the study?

We will offer you the care needed to treat injuries directly resulting from taking part in this research. We may bill your insurance company or other third parties, if appropriate, for the costs of the care you get for the injury, but you may also be responsible for some of them.

There are no plans for the University of Pennsylvania to pay you or give you other compensation for the injury. You do not give up your legal rights by signing this form.

If you think you have been injured as a result of taking part in this research study, tell the person in charge of the research study as soon as possible. The researcher's name and phone number are listed in the consent form.

When is the Study over? Can I leave the Study before it ends?

This study is expected to end after all participants have completed all visits, and all information has been collected. This study may also be stopped at any time by your physician, the study Sponsor, or the Food and Drug Administration (FDA) without your consent because:

- The Primary Investigator feels it is necessary for your health or safety. Such an action would not require your consent, but you will be informed if such a decision is made and the reason for this decision.
- You have not followed study instructions.
- The Sponsor, the study Principal Investigator, or the Food and Drug Administration (FDA) has decided to stop the study.

If you decide to participate, you are free to leave the study at any time. Withdrawal will not interfere with your future care. If you choose to withdraw from the study, you will be asked to attend an Early Termination visit in which we will take your vital signs, perform a pill count, check your blood levels, complete a medical history and physical, and get any information regarding side effects you may be experiencing at that time.

Who can see or use my information? How will my personal information be protected?

We will do our best to make sure that the personal information obtained during the course of this research study will be kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law.

If information from this study is published or presented at scientific meetings, your name and other personal information will not be used. If this study is being overseen by the Food and Drug Administration (FDA), they may review your research records.

The research team will make every effort to keep all the information you tell us during the study strictly confidential, as required by law. Any documents you sign, where you can be identified by name will be kept in a locked file cabinet in Dr. Zamani's research space in the Penn Presbyterian Research Center. All of your electronic information will be kept in a secure server and the file that contains your health information will not be the same as the file that contains your name. Only the investigators will have access to the codes that link your health information with your personal data. These documents will be kept confidential.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

Electronic Medical Records and Research Results

What is an Electronic Medical Record and/or a Clinical Trial Management System?

An Electronic Medical Record (EMR) is an electronic version of the record of your care within a health system. An EMR is simply a computerized version of a paper medical record.

A clinical trial management system (CTMS) is used to register your information as a participant in a study and to allow for your research data to be entered/stored for the purposes of data analysis and any other required activity for the purpose of the conduct of the research.

If you are receiving care or have received care within the University of Pennsylvania Health System (UPHS) (outpatient or inpatient) and are participating in a University of Pennsylvania research study, information related to your participation in the research (i.e. laboratory tests, imaging studies and clinical procedures) may be placed in your existing EMR maintained by UPHS. Information related to your participation in clinical research will also be contained in the CTMS.

If you have never received care within UPHS and are participating in a University of Pennsylvania research study that uses UPHS services, an EMR will be created for you for the purpose of maintaining any information produced from your participation in this research study. The creation of this EMR is required for your participation in this study. In order to create your EMR, the study team will need to obtain basic information about you that would be similar to the information you would provide the first time you visit a hospital or medical facility (i.e. your name, the name of your primary doctor, the type of insurance you have). Information related to your participation in the study (i.e. laboratory tests, imaging studies and clinical procedures) may be placed in this EMR.
Once placed in your EMR or in the CTMS, your information may be accessible to appropriate UPHS workforce members that are not part of the research team. Information within your EMR may also be shared with others who are determined by UPHS to be appropriate to have access to your EMR (e.g. health insurance company, disability provider, etc.).

What information about me may be collected, used or shared with others?

- Name
- Address

- Telephone number
- Date of birth
- Social Security number (for payment purposes)
- Personal and family medical history
- Results from physical examinations, tests or procedures
- Dates of tests or procedures
- Medical record numbers
- Echocardiogram images obtained during the study
- Blood, urine, and saliva samples
- Medication history
- Several questionnaires
- Email address

Why is my information being used?

Your contact information is used by the research team to get in touch with you during the study. Your information and results of tests, procedures, and questionnaires are used to:

- Complete the research.
- Oversee the research.
- Ensure that the research was done right.

Who may use and share information about me?

The following individuals may use or share your information for this research study:

- All research staff directly associated with this trial
- University of Pennsylvania Institutional Review Board (IRB)
- The Sponsor of the trial (University of Pennsylvania)

Who, outside of the School of Medicine, might receive my information?

- University of Pennsylvania Institutional Review Board (IRB)
- **Oversight organizations**
- The Food and Drug Administration (FDA)
- The Office of Human Research Protections (OHRP)

Once your personal health information is disclosed to others outside the School of Medicine, it may no longer be covered by federal privacy protection regulations.

The Principal Investigator or study staff will inform you if there are any additions to the list above during your active participation in the study. Any additions will be subject to University of Pennsylvania procedures developed to protect your privacy.

How long may the School of Medicine use or disclose my personal health information?

Your authorization for use of your personal health information for this specific study does not expire.
Your information may be held in a research database. However, the School of Medicine may not re-use or re-disclose information collected in this study for a purpose other than this study unless:

- You have given written authorization.
- The University of Pennsylvania's Institutional Review Board grants permission.
- As permitted by law.

Can I change my mind about giving permission for use of my information?

Yes. You may withdraw or take away your permission to use and disclose your health information at any time. You do this by sending written notice to the investigator for the study. If you withdraw your permission, you will not be able to stay in this study.

What if I decide not to give permission to use and give out my health information?

Then you will not be able to be in this research study.

You will be given a copy of this Research Subject HIPAA Authorization describing your confidentiality and privacy rights for this study.

By signing this document you are permitting the School of Medicine to use and disclose personal health information collected about you for research purposes as described above.

The study doctors believe that there may be opportunities in the future with other studies in HFpEF. We would like your permission to contact you in the future. Please initial below if you agree to being contacted by telephone in the future (for up to 3 years after your final visit) about additional studies related to HFpEF.

_____: I agree to being contacted in the future about studies related to findings in this study.
_____: I do not agree to be contacted in the future about studies related to findings in this study.

If you should change your mind about someone contacting you in the future, you will need to send a written letter to the study team at the address on the first page of this consent form.

If you have been approached to participate in this study at the University of Pennsylvania or CMCVAMC centers, you will also be asked if you are interested in participating in the cardiac MRI sub-study that was described earlier, and involves undergoing stress test of the heart using a MRI machine.

I agree to participate in the sub-study: Yes _____ No_____

Who can I call with questions, complaints or if I'm concerned about my rights as a research subject?

If you have questions, concerns or complaints regarding your participation in this research study or if you have any questions about your rights as a research subject, you should speak with the Principal Investigator listed on page 1 of this form. If a member of the research team cannot be reached or you want to talk to someone other than those working on the study, you may contact the Office of Regulatory Affairs with any question, concerns or complaints at the University of Pennsylvania by calling (215) 898-2614.

Disclosure of Interest

The chair for this research study is named as an inventor on a patent application on the concept of using potassium nitrate for the treatment of heart failure with preserved ejection fraction. Therefore, the researcher could benefit financially from the results of this research study. The Principal Investigator at the University of Pennsylvania, who will be making all decisions about your safe participation in the study, does not have any financial conflicts of interest. If you would like more information, please ask the researchers or the study coordinator.

When you sign this form, you are agreeing to take part in this research study. This means that you have read the consent form, your questions have been answered, and you have decided to volunteer. Your signature also means that you are permitting the University of Pennsylvania to use your personal health information collected about you for research purposes within our institution. You are also allowing the University of Pennsylvania to disclose that personal health information to outside organizations or people involved with the operations of this study.

A copy of this consent form will be given to you.

_____	_____
Name of Subject	Signature of Subject Date (Please Print)
_____	_____
Name of Person Obtaining	Signature Date Consent (Please Print)