NCT #: NCT03483051

Title: Targeting Pulsatile Load to Increase Exercise Capacity and Quality of Life After Aortic Valve Replacement for Severe Aortic Stenosis (PULSE AS)

Date: 02-Aug 2018

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

Protocol Title:	Targeting Pulsatile Load to Increase Exercise Capacity and Quality of Life After Aortic Valve Replacement for Severe Aortic Stenosis (PULSE AS)
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Why am I being asked to volunteer?

You are being invited to participate in a research study because you recently had an aortic valve replacement for aortic stenosis. Our goal is to look at the effects of potassium nitrate on your health. 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 and quality of life in people who recently had an aortic valve replacement for aortic stenosis. After aortic valve replacement, some patients continue to be 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 who have aortic stenosis develop problems with their arteries that affect their ability to exercise. potassium nitrate has been shown to improve blood flow in the body in healthy individuals. We would like to now study these pills in patients in who recently had an aortic valve replacement for aortic stenosis.

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 9 weeks. The study involves 3 visits to our research center. The details of the visits are outlined below. We will enroll approximately 22 individuals in this 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 scheduled visits; there may be additional visits if you experience any side effects. During each visit, 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 4 weeks ***(Intervention Phase 1)***. At the end of that period, 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 approximately 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 period of approximately 4 weeks. At the end of this second 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 endpoint assessment.

This study is a crossover study, which means that over the course of the study, all participants will receive both the “active” study medication, KNO_3, and the “control,” which is a study medication that has no known actions on your blood vessels. The control 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.

Procedures and Visit Schedule

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, you will be randomized to study medications for the initial period ***(Intervention Phase 1)***.

During this visit, we will give you a questionnaire about your symptoms. We will also perform a physician 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. We will also perform orthostatic blood pressure measurements, where your blood pressure will be assessed both while lying down and with standing.
- *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 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 a saliva (spit) and a urine sample.
- *Questionnaires* –We will 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)
- *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 objective 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 (Actigraph device)*- 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 on your wrist as much as possible for one week prior to your return visit 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.
- *Randomization* - After baseline testing is complete, you will be randomly assigned to receive either potassium nitrate or control first. You will not be told which medication you are getting.

At the end of this visit, you will be given study medications to be taken **twice daily** during **Intervention Phase 1.**

~1 week phone call: We will call you after approximately 1 week to see how you are doing. If you are feeling well, we will then increase the dose to **three times a day. Medication should 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. We will ask you to take study medications for approximately 4 weeks.

Visit 2*: This visit will occur approximately 4 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. We will place an IV in your arm and check the levels in your blood. 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. We will then ask you to perform some of the study procedures. About two hours after you have taken the study

medication, we will check your blood levels from your IV and collect another spit sample. We will then ask you to perform the rest of the study procedures, as listed below.

List of Visit #2 Procedures:

- *Brief interval history, review of all medications you are taking*
- *Vital Signs (including orthostatic blood pressure measurement) and brief Physical Exam*
- *Light breakfast with study medication*
- *Questionnaires* – We will ask you about any potential side effects you may be experiencing from the study medication. We will also administer the questionnaire asking about your symptoms (Kansas City Cardiomyopathy Questionnaire).
- *Blood Draws from IV and saliva and urine samples*
- *Arterial Tonometry*
- *Doppler Echocardiogram*
- *Bicycle Exercise Test with peak exercise blood sample*
- *Arterial dilation assessment*

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 that 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. 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.

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.

Arterial dilation assessment: We will take pictures of the artery in your arm using ultrasound. We will then inflate a blood pressure cuff wrapped around your forearm for 5 minutes. This may make your hand feel “pins and needles” or heavy. This may be slightly uncomfortable for you, but there is no serious harm to this. We will then deflate

the blood pressure cuff and measure the increase in blood flow as blood rushes into your forearm and hand. We will measure how your artery responds (dilates) in response to this inflation, using ultrasound. None of these devices are associated with any known side effects. You may, however, notice slight bruising on your arm from the blood pressure cuff, though this will not last long.

Other tests (in an identical fashion to visit 1):

- *Vital Signs (including orthostatic blood pressure measurement)*
- *Questionnaires* – We will ask you about any potential side effects you may be experiencing from the study medication. We will also administer the questionnaire asking about your symptoms (Kansas City Cardiomyopathy Questionnaire).
- *Blood Draws from IV and saliva and urine samples*
- *Arterial Tonometry*
- *Doppler Echocardiogram*

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 ± 3 days 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 control, 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 control, though the subjects may receive these medications in a different order.

~1 week phone call: We call you after about one week of taking the **Intervention Phase 2** study medications twice a day. We will discuss how you are feeling 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 4 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. We will place an IV in your arm and check the levels in your blood. 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. We will then ask you to perform some of the study procedures. About two hours after you have taken the study medication, we will check your blood levels from your IV and collect another spit sample. We will then ask you to perform the rest of the study procedures, as listed below.

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

- *Brief interval history, review of all medications you are taking*
- *Vital Signs (including orthostatic blood pressure measurement) and brief Physical Exam*
- *Light breakfast with study medication*
- *Questionnaires* – We will 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*
- *Arterial Tonometry*
- *Doppler Echocardiogram*
- *Bicycle Exercise Test with blood sample at peak exercise*
- *Arterial dilation assessment*

***Your participation is complete after Visit 3*.** We will compare your results from Visit 2 and 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 with EKG and vital signs.** • Complete a **questionnaire on your symptoms** • Have your **blood drawn, an IV placed, and give a saliva and urine sample.** • The **Arterial Tonometry** test. • Have a **Doppler Echocardiogram.** • **Have a 6-minute walk test** **If you meet all of our criteria, we will mail the medications to you after reviewing your laboratory studies (*Intervention Phase 1). We will also mail you the activity monitor to wear for the one-week immediately prior to your return visit.***
Visit 2 (after ~4 weeks of study medications)	• Record **Vital Signs.** • Retrieve the **activity monitor** 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. • Complete a **questionnaire on your symptoms.** • Discuss **potential side effects.** • **Arterial dilation assessment** *~ After 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**

	After visit 2, you will start the ~ 1-week washout period during which you will NOT take any study medication. Please continue your other medications. ***After this washout period, you will start Intervention Phase 2 study medications which you will receive by mail. We will also mail you the activity monitor to wear for the one-week immediately prior to your return visit.***
Visit 3 (after ~4 weeks of Intervention Phase 2 study medications)	• Record **Vital Signs.** • 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. • Complete a **questionnaire on your symptoms.** • Discuss **potential side effects.** • **Arterial dilation assessment** *~ After 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.** • Return your activity monitor ***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 who recently had an aortic valve replacement for aortic stenosis. 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
- Fatigue
- 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 African, Asian or Mediterranean decent, we will make sure that you don’t have Glucose-6-phosphate dehydrogenase (G6PD) deficiency, which would make you more susceptible to methemoglobinemia.

We did not see any serious side effects from potassium nitrate in previous studies. 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 who recently had an aortic valve replacement for aortic stenosis. You are not eligible for this study if you are on other nitrate-containing medications such as isosorbide mononitrate (Imdur) or isosorbide dinitrate (Isordil). You are also not eligible for this study if you are taking allopurinol (Zyloprim) or febuxostat (Uloric, Adenuric) for gout, as these drugs may interfere with activation of the study medication.

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. We will discuss your diet and 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 (Imdur), isosorbide dinitrate (Isordil, Dilatrate).
- 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.
- We will go over 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 and groin. This will feel like someone is taking your pulse in the neck 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

- 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. Individuals who are trained to respond to situations that might develop during exercise will closely monitor you throughout the exercise period. It is expected that you will become tired and short of breath during this exercise test, as we do ask that you push yourself to the most that you can possibly do.
- 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. 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 your heart 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.

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, you will be discontinued from the trial, but we will collect information about the pregnancy and its outcome via telephone call.

Risks of Genetic Testing

This research includes genetic testing. We will be measuring how your body changes its expression of different genes over the course of this study. 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.

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 will be handled in a way that cannot be linked to your name or other personal information. Only the investigator and study staff will have access to the list that connects your name to your data.

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. Anupam Kumar at 267-293-9247.

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.

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 or prepaid card (GreenPhire ClinCard). We will follow the following reimbursement scheme:

- Completion of Visit #1: $100
- Completion of Visit #2: $150
- Completion of Visit #3: $150

The maximum total amount (if you complete all study visits) will be $400. You will be paid for each visit that you complete. Your reimbursement will be mailed out as one check approximately 4-8 weeks after each visit is completed.

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, 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. Kumar's research office. 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)
- University of Pennsylvania Office of Clinical Research (OCR)
- Other research personnel with access to the databases for research and/or study coordination and as otherwise approved by the IRB

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 aortic stenosis. 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.

_____: 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.

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.

The person leading this medical research study, Dr. Chirinos, 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 but not for aortic stenosis. Therefore, the researcher cannot benefit financially from the results of this research study. 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 (Please Print)	Signature of Subject	Date
_____	_____	
Name of Person Obtaining Consent (Please Print)	Signature	Date