STUDY PROTOCOL

Official title: Reduction of Cardiac Steatosis and Improvement of Diastolic Function by Modulating Metabolic Health in Obese Individuals

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The University of Texas Southwestern Medical Center at Dallas
Institutional Review Board

PROJECT SUMMARY

Principal Investigator: Satyam Sarma

Study Title: Reduction of Cardiac Steatosis and Improvement of Diastolic Function by Modulating Metabolic Health in Obese Individuals

Sponsor/Funding Source: American Heart Association
Project Study Title: Novel HFpEF Prevention Strategies In High Risk Individuals: High Intensity Exercise Training Plus Omega-3 Fatty Acids

Purpose:
The purpose of this study is to determine whether 1 year of supervised exercise training in obese individuals at high risk for developing HF, incorporating high intensity interval training (HIIT) two to three times per week in conjunction with daily oral administration of omega-3 poly-unsaturated fatty acids will lead to reduction in visceral adiposity, regression of myocardial triglyceride levels and improvements in cardiac diastolic and vascular function.

Objectives:
The global objective of this project is to test novel strategies to prevent obesity related abnormalities in diastolic function that may progress to heart failure with preserved ejection fraction (HFpEF). These include: a) identifying high risk individuals by using population derived imaging and blood biomarkers; and b) implementing novel exercise training and "nutri-ceutical" strategies in obese middle aged individuals with high amounts of visceral fat, an important risk factor in the development of heart failure and adverse cardiac remodeling.

The PI's previous research has demonstrated that: a) high levels of myocardial triglyceride content are associated with a smaller and less distensible left ventricle with reduced tissue relaxation rates compared to those with low levels and b) low fitness and high body mass index were the strongest predictors of elevated myocardial content. Work by the PI's collaborators have shown the consequences of excess visceral adiposity (intra- and retro-peritoneal adipose tissue) on cardiac remodeling suggesting individuals with high visceral fat content and low fitness are at particularly high risk for HF.

The primary objective of this project, which reflects specific aim 2 of Drs. Levine/Sarma's AHA grant, is therefore to identify high risk, sedentary, middle aged obese individuals with high visceral fat levels, and initiate an exercise program in conjunction with omega-3 fatty acid supplementation designed to reduce visceral adiposity and regress myocardial triglyceride accumulation. Findings from this aim would have enormous public health significance and establish a novel, practical exercise training program and "nutria-ceutical" strategy to reverse obesity related cardiovascular remodeling.

Hypothesis:
High aerobic exercise training in conjunction with daily omega-3 supplementation will reduce visceral myocardial triglyceride accumulation by reducing visceral adiposity. A reduction of myocardial fat will lead to improved LV structure and diastolic function by an approach that is not necessarily predicated on weight loss.
Specific Aim:
To test our hypothesis that reduction in myocardial triglyceride content will improve markers of

diastolic function, we have designed a randomized, double blind, placebo controlled trial. We will study four groups of previously sedentary obese middle aged subjects at high risk for development of HF for one year with the following interventions: A) sedentary controls taking placebo; B) sedentary subjects taking omega-3 fatty acids; C) subjects undergoing high intensity aerobic exercise training while on placebo and D) subjects undergoing high intensity aerobic exercise training while taking omega-3 fatty acids. Subjects will be categorized as high risk and enrolled on the basis of elevated serum biomarkers (cTnT) and high visceral fat content (>2.5 kg). We will perform comprehensive non-invasive assessments of cardiovascular structure and systolic/diastolic function before and after 1 year of an exercise intervention involving high intensity intervals and omega-3 administration. We anticipate the combination of high intensity aerobic exercise in conjunction with high dose omega-3 supplementation will reduce visceral adiposity, decrease myocardial triglyceride content and improve markers of diastolic and vascular function.

Background:

Obesity is an independent risk factor for the development of heart failure (HF). While frequently associated with co-morbid conditions of coronary artery disease, hypertension and obstructive sleep apnea, patients with obesity are twice as likely to develop heart failure compared to lean controls even after adjusting for baseline differences. The mechanisms responsible for the increased prevalence of HF amongst obese individuals is unknown but thought to arise from a multitude of cardiovascular structural changes that occur in obesity including increased left ventricular mass and chamber size, abnormalities in diastolic relaxation, increased ventricular filling pressures, decreased cardiac strain and contractile function, increased deposition of intra-myocardial triglycerides and increased aortic stiffness. Even in the absence of overt hypertension and other co-morbid conditions, obese individuals show signs of subclinical LV dysfunction, factors that likely predispose to the development of HF, particularly HF with preserved ejection fraction (HFpEF). The high prevalence of obesity in HFpEF patients: approximately one third are obese (BMI > 30 kg/m2) and over 80% who are overweight (BMI > 25 kg/m2); underscores the important relationship between increased body mass and cardiac dysfunction.

However, the impact of obesity on cardiac function cannot be attributed to an increase in body weight alone. Adipose tissue is a highly active endocrine organ that secretes adipokines, circulating signaling molecules (e.g. leptin, TNF-a, PAI-1) that strongly influence whole body metabolism and regulate insulin sensitivity, ectopic fat deposition, and endothelial function. The distribution and location of adipose tissue, specifically visceral fat, is associated with the prevalence of cardiovascular disease suggesting that not all fat behaves equally in conferring cardiovascular risk. Previous work by our group and others have shown different locations of fat depots have differing effects on LV structure, with visceral fat independently associated with smaller LV cavity dimensions and increased wall thickness. The mechanism mediating these changes is unknown but may be related to accumulation of intra-myocardial triglycerides, which we have linked to decreased ventricular distensibility and abnormal diastolic filling parameters. Overall “metabolic health” may also be important: even in non-obese, non-diabetic individuals with metabolic syndrome, the risk of developing HF is ~ 2.5 fold higher than those who are obese but otherwise metabolically healthy.

With the global pandemic of obesity growing to larger proportions and with close to one quarter of US adults meeting the criteria for metabolic syndrome (MetS), more targeted and sustainable strategies to reverse the cardiac burdens imposed by excess body adiposity are needed. Current approaches focus on the individual components of the metabolic syndrome and treat underlying hypertension and lipid abnormalities. Despite the success of these interventions in correcting specific components of MetS, the incidence of hyperglycemia and abdominal obesity continue to rise highlighting the incompleteness of current therapies in addressing the root problem of high visceral adiposity. If left unchecked, the high prevalence of abdominal obesity could lead to a dramatic rise in new cases of HF, especially HFpEF a condition that has no proven therapies.

Interventions designed to improve metabolic health and increase lean body mass in obese patients with high levels of visceral adiposity may restore myocardial mechanics and reduce the future risk of developing HF. Exercise training in particular can be an effective means of improving cardiac function in obesity with small studies showing improvements in LV longitudinal strain, diastolic function and reductions in indexed LV mass. Designing an exercise program that specifically targets metabolic parameters and reduces visceral adiposity may be more effective in reversing cardiovascular abnormalities associated with abdominal obesity than traditional aerobic exercise alone.

To supplement exercise training, we also propose adding high dose (2 grams/day) omega-3 PUFA to aid in metabolic remodeling. PUFA, administered in the form of fish oil, can increase fatty acid oxidation, increase lean body mass while decreasing fat mass. When combined with moderate aerobic exercise, PUFA can potentiate fat mass loss and decrease triglyceride/HDL-c ratios. Complementing HIIT with daily omega-3 PUFA administration may improve body composition and cardiovascular remodeling than either intervention alone.

The primary objective of this application is therefore to identify middle aged (age 40 – 60), sedentary, obese individuals with high levels of visceral adiposity (>2.5 kg), elevated biomarkers of cardiac injury (high sensitivity troponin) or wall stress (NTBNP), and initiate an exercise program designed to reduce visceral fat content and regress myocardial triglyceride accumulation. We hypothesize that modulating metabolic parameters associated with adverse cardiac remodeling will improve LV structure and function by an approach that is not necessarily predicated on weight loss. After this aim is accomplished, we will have established a novel approach to reversing diastolic and vascular abnormalities associated with obesity which may ultimately lead to HFpEF prevention in a high risk population. Such a determination would have enormous public health significance since this condition is quite difficult to treat once established.

Concise Summary of Project:

Experimental Design and Methods:

To test the hypothesis that 1 year of exercise training in conjunction with daily oral administration of omega-3 poly-unsaturated fatty acids in obese individuals at high risk for developing HF will regress myocardial triglyceride content and improve cardiac function, we have designed a randomized, double blind, placebo controlled trial. We will study four groups of previously sedentary obese middle aged subjects for one year with the following interventions: A) sedentary controls taking placebo; B) sedentary subjects taking omega-3 fatty acids; C) subjects undergoing high intensity aerobic exercise training while on placebo and D) subjects undergoing high intensity aerobic exercise training while taking omega-3 fatty acids. We will perform comprehensive non-invasive assessments of cardiovascular structure and function in all groups before and after 1 year of training.

Subject Population:

Subjects for this specific aim will be recruited from the Dallas Heart Study (DHS), a population based, probability sample of 6,101 individuals in the Dallas community, used by the PI in the previous studies. Approximately 250 individuals meet inclusion criteria for our study and have 1) ejection fraction >0.50; 2) >2.5 kg visceral fat (intra- and retro-peritoneal adipose tissue) documented by MRI; 3) either a positive high sensitivity troponin, or NTBNP in the 4th quartile of the DHS; 4) age range 40 -60 and 5) BMI range 30 – 50. All these subjects will be sent a letter followed up by a telephone call as we have done previously. Interested volunteers will be invited to the laboratory for consent, screening and familiarization. The advantages of this population include: a) the presence of a multi-ethnic sample oversampled for African-Americans, assuring a high likelihood for inclusion of sufficient ethnic minorities; b) recruitment from a database including individuals already favorably disposed to and experienced in cardiovascular research; c) clear documentation that all volunteers approached for the study are at high risk for the development of HFpEF; d) the use of a probability based design assuring a representative sample of the individuals in the appropriate age ranges free of biases associated with self-selected volunteers. This approach facilitates making inferences from the data at the population level

(high external validity).

If we are unable to recruit our target population from this data base, we will enrich our sample by recruiting from the Cooper Clinic Longitudinal Study (CCLS; formerly called the Aerobics Center Longitudinal Study), a cohort of >80,000 individuals in whom physical activity and cardiovascular risk factors have been carefully quantified and followed for >40 yrs. Dr. Levine and Dr. Sarma have a close working relationship with CCLS investigators. A subset of this population (N=~ 3,000) has had echocardiography and we propose to limit our recruitment efforts to men and women of the same age range of the DHS, that are identified as low fit and obese. We estimate that ~ 4 – 8% of these subjects will be obese and have an elevated high sensitivity cTnT or NT-BNP as well as high visceral adiposity. Given our previous track record of recruitment from these two data bases (DHS and CCLS) we fully expect to be able to recruit our proposed subject numbers. However if for some reason we still have not recruited our full cohort, we will expand our recruitment to include employees of Texas Health Resources and University of Texas Southwestern Medical Center. The combined institutes consist of >40,000 employees. Assuming a similar obesity rate to the general population of 35%, half of whom have high levels of visceral adiposity, we anticipate a significant number of employees will qualify for our study.

Subjects will be excluded if they have a history of heart failure, coronary ischemia, prior cerebrovascular disease, permanent atrial fibrillation and active/recent tobacco use (< 5 years since cessation). Potential subjects will be excluded if they are unable to participate in intensive aerobic exercise (e.g. orthopedic limitations) or unable to undergo MRI. Please see "criteria for subject exclusion" section below for more details.

Study design:

To test the hypothesis that reduction in myocardial triglyceride content will improve markers of diastolic function, we have designed a randomized, double blind, placebo controlled trial. To recap, we will study four groups of previously sedentary obese middle aged subjects at high risk for development of HF for one year with the following interventions: A) sedentary controls taking placebo; B) sedentary subjects taking omega-3 fatty acids; C) subjects undergoing high intensity aerobic exercise training while on placebo and D) subjects undergoing high intensity aerobic exercise training while taking omega-3 fatty acids. We anticipate the combination of high intensity aerobic exercise in conjunction with high dose omega-3 supplementation will reduce visceral adiposity, decrease myocardial triglyceride content and improve markers of diastolic and vascular function.

We will need to complete baseline testing on 80 subjects to enter the 1 year intervention with 44 assigned to exercise and 36 to yoga control. This difference is designed to account for differences in compliance within the 2 exercise groups. Within each exercise/yoga group, half of subjects will be randomized to placebo or omega-3 fatty acid supplementation. For the exercisers, 22 subjects will be given placebo and 22 will be given omega-3. For the yoga control, 18 will receive placebo and 18 will receive omega-3. Ultimately the study is powered to end up with 15 subjects per group (total N=60) accounting for drop outs to complete all follow up testing (please see "power calculations" section on page 697 (of 731) of the AHA grant, submitted as "protocol" which develops and supports these numbers in some detail).

However, not every subject who enrolls in the study will go onto complete testing. During testing, exclusion criteria may be identified requiring disqualification from the study; examples include the identification of coronary artery disease by cardiopulmonary stress testing. Furthermore, subjects may wish to withdraw from testing for personal or health related reasons. This requires "enrolling", or consenting, a total of 120 subjects. We plan to enroll these 120 subjects over an 18-month period and will halt enrollment after 80 volunteers have completed all pre-testing as described above. Ideally, our protocol can be completed in 12-14 months; however, unexpected interruptions occasionally occur, extending the protocol up to as much as 24 months. With these delays taken into consideration, we expect to conclude our study in roughly 36 months (3 years). All enrollment and testing will be performed at our facility, making this a

single site study.

Following completion of the baseline studies, volunteers will be randomized to either an exercise intervention, or yoga/Tai Chi control. Subjects will be stratified by sex and allocated to the either exercise or yoga intervention using a stratified block randomization at a 1.2 to 1 exercise to yoga ratio (allowing for greater attrition for the exercise group). The randomization schema will be programmed using SAS Proc Plan and performed by Ms. Beverly Huet, a biostatistician on our team. An active yoga/Tai Chi control allows for equipoise for the volunteers by improving quality of life without affecting fitness. It also controls for the contact with study staff; we are using this approach for the non-exercise controls in our current clinical trial (NCT02039154).

For the exercise group, workouts may vary depending on subject preference (walk, cycle or rowing ergometer). For the first four weeks, subjects will perform low intensity exercise (~50-60% maximal predicted heart rate) for 20 – 30 minutes 3 – 4 times per week to familiarize themselves with equipment, operation of heart rate monitors and develop a habitual exercise schedule. After 4 weeks, subjects will then begin HIIT sessions once per week, increasing to twice weekly after 4 weeks. For HIIT sessions, subjects will warm up at light to moderate intensity for 10 minutes before starting interval exercise (90-95% of maximum HR or Borg scale of 17-18) for four minutes followed by an active recovery period (50-60% of maximum HR) of 4 minutes. Each interval session will comprise 4 cycles (interval/recovery) for a total exercise time of 32 minutes not including warm up. For the remaining 10 months (for a total exercise intervention duration of 12 months), subjects will be required to perform 2 HIIT sessions per week but encouraged to do 3 sessions if possible. Once they have started HIIT, subjects will not be required to continue with low intensity exercise sessions but may do so on their own accord. An experienced exercise physiologist will directly monitor the first few HIIT sessions. Subjects will work closely with their assigned physiologist and review heart rate monitor logs to ensure proper performance of HIIT.

For the yoga group, subjects will be encouraged to participate in yoga/tai chi/pilates classes at the Finley Ewing Cardiovascular Center at Texas Health Resources Dallas, or a gym/recreation center of their choice that is approved by one of the exercise physiologists on the research team. The goal for this group is exercise classes that will be of benefit to them, but that will not include sustained aerobic, endurance exercise. In place of a group exercise class, subjects will have the option of purchasing videos for home use. The subjects will be encouraged to participate in some form of non-endurance training at least 3 days per week. Each subject will receive an exercise log in which they will be expected to record their training.

The dosage of omega-3 supplementation will be 2 grams once daily and provided in the form of prescription strength Lovaza, a commercially available pharmaceutical used in the treatment of hypertriglyceridemia. Typical dosage for Lovaza in clinical use is 4 grams daily or divided twice daily. We have chosen 2 grams once daily on the basis of prior studies using omega-3 to improve lean body mass and fatty acid oxidation rates. Omega-3 fatty acids are a commonly used over-the-counter supplement and in numerous clinical trials have been shown to be safe with minimal side effects. Please see "potential risks" section for more detail regarding drug safety profile. For patients assigned to placebo, an identical appearing gel capsule containing olive oil will be given in a dosage of 1 gram daily.

Study Procedures:

Five subjects, enrolled using an abbreviated informed consent, will participate in testing the MRI protocol developed for the primary study.

Overview: Once a subject has enrolled in our study, he or she will undergo a comprehensive set of "Baseline Testing", one year of the experimental intervention (i.e. randomization into one of

the groups as described above) and a comprehensive set of "Follow-up Testing" at the conclusion of the intervention. The "Experimental Intervention" has been described in detail in the STUDY DESIGN section of this document and will be briefly reviewed below. The "Baseline Testing" and "Follow-up Testing" protocols are similar and are described in detail below.

"Baseline Testing" Procedure: The baseline testing procedure begins with a screening visit. If all inclusion criteria are met and no exclusion criteria are identified, the subject will be given the option to enroll in the study. After enrolling in the study, additional demographic information is obtained and Study Day 1, Study Day 2, and Study Day 3 are scheduled.

"Baseline" Screening Procedure: To determine whether a subject has interest and is eligible for our study, the first visit will be dedicated to screening. During this visit, we will obtain: informed consent, a medical history and physical exam, a screening electrocardiogram and a screening echocardiogram. Furthermore, we will begin the process of obtaining additional demographic data including: a) 24 hour ambulatory blood pressure monitor to most precisely measure baseline blood pressure and its circadian variability; and b) routine blood work (serum chemistries). This visit will usually last between 2-2.5 hours; it involves one blood draw of approximately 4 tablespoons.

In addition to the screening visit described above, each subject will go through a standard protocol consisting of 3 days of testing, separated by at least 72 hrs, but no more than 4 wks between tests:

"Baseline" Day 1: This visit consists primarily of a maximal exercise test and a screening echocardiogram with the measurement of echo derived wall motion and systolic volumes, blood pressure, ECG, heart rate, oxygen uptake, cardiac output (acetylene rebreathing method), stroke volume, total peripheral resistance, and a-vO2 difference. Goals of this day are to: 1) estimate the peak VO2 and 2) carefully assess for the presence of provocable ischemia via both ECG and contractile imaging. This visit will usually last between 1.5 - 2 hours; no blood draws are performed during this visit.

"Baseline" Day 2: This visit consists of three different studies. It will last approximately 4.5 hours.

1) Submaximal and maximal exercise test: Measurements of blood pressure, ECG, heart rate, oxygen uptake, cardiac output (acetylene rebreathing method), stroke volume, total peripheral resistance, and a-vO2 difference will be done during the exercise test. Goals of this day are to: 1) quantify the augmentation of SV during submaximal exercise, 2) precisely measure the VO2max; and 3) determine the relationship between cardiac output. There are no blood draws performed during this study; however, 3 fingersticks are performed to measure lactate at various stages of the submaximal and maximal exercise testing.
2) Arterial compliance testing: Used to determine the flexibility of the arteries. We will obtain blood pressure measurements through several different non-invasive techniques and take pictures of the arteries using ultrasound. The arteries that we will examine include the arteries in the wrist, elbow, neck, groin, and stomach. We will also collect approximately 4 tablespoons of blood to measure serum biomarkers of cardiac and metabolic health.
3) Body composition analysis: Used to determine the body's muscle, fat, and water composition using skin caliper technique and underwater weighing techniques. First, we will obtain detailed measurements of height, weight, skinfold thickness, etc., using measuring tape and calipers. There is no risk with this procedure, though some individuals experience some pinching from the calipers. We will also measure body composition using DEXA scanning. There is very low dose radiation associated with the

scan, about 1/10th the dose of an x-ray. Prior to a DEXA, we will perform a routine pregnancy test to ensure that subjects are not pregnant before undergoing the scan.

"Baseline" Day 3: Magnetic Resonance Imaging - The 3rd day is devoted to MRI, and includes measurements of LV mass, aortic compliance, MR spectroscopy for the assessment of myocardial triglyceride concentration, and delayed enhancement imaging for quantification of fibrosis. We have developed an integrated protocol which starts with the anatomic images for measurements of cardiac and vascular morphology followed by spectroscopy for triglyceride content. This visit will usually last between 3-4 hours; no blood draws are performed during this visit.

Experimental Intervention:
The experimental intervention involves randomization into one of four groups. This randomization is designed to assess the impact of omega-3 fatty acids and high intensity aerobic exercise training versus placebo. A more detailed description of the "Experimental Intervention" is included in the STUDY DESIGN section of this document.

"Mid Progress Testing" Procedure: At 6 months into the experimental intervention, subjects will return to the lab for mid-progress testing. This day is identical to "baseline day 2" and allows us to gauge adequacy of the exercise training intervention as well as to assess changes in body composition.

"Follow-up Testing" Procedure: At the conclusion of the one year experimental intervention, follow-up testing will be performed to assess the effects of the intervention. The "Follow-up Testing" protocol is similar to "Baseline Testing" with the omission of the "Baseline" Screening Procedure and "Baseline" Study Day 1.

"Follow-up" Day 1: This day is identical to "Baseline" Day 2 with the additional measurement of 24 hour ambulatory blood pressure.
"Follow-up" Day 2: This day is identical to "Baseline" Day 3.

At the conclusion of the "Follow-up Testing", each subject will have completed our study and reimbursement will be distributed.

Regarding the storage of blood samples, we will retain whatever blood is left over after all the analyses are complete in case other blood tests become available that might be useful to explain the effects of aging and obesity on the heart. The samples will be kept in the freezer in the biochemistry lab at the IEEM with a code to specify from which patient it comes and the study date. Only the Principal investigator and biochemistry lab staff will have access to these samples.

Criteria for Inclusion of Subjects:
One hundred twenty healthy, sedentary men and women ages 40-60 will be recruited to start the intervention on 80 who complete all baseline testing. The key inclusion and exclusion criteria are as detailed in the SUBJECT POPULATION section above. To recap, subjects will be recruited based on 1) the presence of high visceral adiposity (>2.5 kg) assessed by either MRI or DEXA scan, 2) a normal ejection fraction (>50%); 3) elevated serum biomarkers of sub-clinical cardiac injury (cardiac troponin T, brain-type natriuretic peptide) and 4) obesity with BMI range 30 – 50 kg/m^2. Subjects will be recruited from the DHS and CCLS without regard to race or gender.

Criteria for Exclusion of Subjects:
Exclusion criteria include age < 40 or > 60, body mass index > 50, < 30 kg/m^2 and any history of insulin dependent diabetes, heart failure, myocarditis, restrictive cardiomyopathy, permanent/persistent atrial fibrillation, severe chronic obstructive pulmonary disease, unstable coronary artery disease or recent (<12 month) acute coronary syndrome, cerebrovascular disease as evidenced by prior transient ischemic attack or stroke and active/recent tobacco use (quit < 5

years). Female patients will be excluded if they are pregnant or plan to become pregnant (expected rare occurrence in the selected age range of 40 – 60). Patients will be excluded if they are taking non-statin lipid lowering agents (fibrates, niacin, or fish oils) or are unable to exercise. Subjects will also be excluded if they have any contra-indications to MRI including heart pacemaker/internal cardiac defibrillator, heart valve replacement, aortic clips, any metal fragments in the body, brain clips or pieces of metal used in brain surgery, pieces of metal in the body resulting from work as a sheet-metal worker or welder, clips placed in an internal organ, prosthetic devices, such as middle ear, eye, joint, or penile implants, joint replacement, a hearing aid that cannot be removed, an insulin pump, an intrauterine device (IUD), a shunt or stents, a metal mesh or coil implants, metal plate, pin, screws, or wires, or any other metal implants. Subjects unable to speak English will not be recruited because of the complex experimental studies and the need for precise communication between the volunteers and the research staff to ensure safety. All subjects will undergo stress testing as part of screening and if provocable ischemia is detected, they will be referred to their primary physicians for appropriate follow-up.

Sources of Research Material

Research material will consist of paper, tape, and computer records of physiological signals, as well as echocardiographic images stored on electronic media. For subjects who are referred from the Dallas Heart Study, we receive demographic information including name, age, date of birth, phone number, etc. All data is obtained exclusively for research purposes and will be filed in locked cabinets in the PI's laboratory.

Recruitment Methods and Consenting Process:

Subjects will first be recruited from our IRB approved data base derived from the Dallas Heart Study. In addition, subjects may be recruited from CCLS as detailed in the above section "Subject Population." Subjects will be sent a letter followed up by a telephone call as we have done previously. Interested volunteers will be invited to the laboratory for consent, screening and familiarization at which time a history and physical exam will be performed and the experimental procedures will be explained in full by one of the investigators and research nurse who will witness informed consent. In addition, flyers will be used to recruit volunteers at health fairs, colleges, places of worship, athletic and recreational facilities located within Dallas-Fort Worth area.

Compensation for Subjects

Subjects will be compensated for participating in this study. They will be paid $150 after completion of the "Baseline Testing" involving the cardiac MRI, body composition and exercise tests. As this testing is repeated at the conclusion of the study which usually takes one year, subjects will be paid an additional $150 after completion of the "Follow-up Testing" involving the repeat cardiac MRI, body composition and exercise tests. Subjects will also be paid $100 after the successful completion of every quarter of training. Therefore, if a subject completes all of the testing, they will be paid a total of $700 over roughly one year. If they don't complete all study procedures, they will be paid according to the number of procedures completed.

Potential Risks

There are minimal risks from the study and the most significant risk from this experiment come from exercise testing and fish oil/omega-3 fatty acid use.

A. Exercise testing and training - Exercise testing carries a finite risk of adverse cardiovascular event with < 1/100,000 in well individuals, and approximately 1/10,000 in sick cardiac patients. Exercise training using high intensity aerobic intervals is also safe and has been used in a number of high risk cardiac patients. Previously published studies of high aerobic intensity interval training demonstrated a low risk (1 per 23,000 hours of high intensity exercise) of serious

musculoskeletal injury or cardiovascular complication in patients with coronary heart disease undergoing cardiac rehabilitation. In a relatively healthy subject population free from overt clinical heart disease, we anticipate the risks of interval training will be far less and our group has extensive experience with designing interval regimens that lessen the risk of musculoskeletal injury (NCT02039154). The inclusion of yoga as a control arm will also provide our subjects clinical equipoise, ensuring all participants, whether randomized to aerobic or yoga exercise will derive benefit from a lifestyle training intervention.

B. Fish oil/Omega-3 fatty acid (Lovaza): There is minimal risk from ingesting fish oil/omega-3 at the doses provided in this study. Fish oil at prescription level doses has been used by thousands of patients with very few serious adverse reactions. In 23 clinical trials of Lovaza, side effects occurred in approximately 3% of patients compared to 1% of placebo and most commonly were eructation (4%), dyspepsia (3%) and taste perversion (3%). Some individuals who have a history of bleeding disorders or very low platelets may be at increased risk of suffering minor bleeding (gingival bleeding, skin bruising). Rarely, allergic reactions may occur to the medications contained within the fish oil tablets including GI distress or rash. Although double blinded, all subjects will be closely monitored for adverse reactions including bleeding, bruising, GI distress. In addition, liver function tests and total lipid panel will be checked at baseline and during mid-testing. Rarely, Lovaza may cause an asymptomatic rise in LFTs as well as an increase in LDL-cholesterol. Subjects will be taken off Lovaza if LFTs increase by more than 3x upper limit of normal or if LDL-c increases by more than 50%.

Special Precautions

Exercise testing will be performed by experienced personnel with careful ECG monitoring and with resuscitative equipment immediately available. The test will be stopped if signs or symptoms of ischemia develop, if excessive hypertension or hypotension develops, or if increasing severity and complexity of arrhythmias occurs during exercise.

Procedures to Maintain Confidentiality:

All records including signed consent forms will be kept on file by Dr. Sarma at the Institute for Exercise and Environmental Medicine at Texas Health Presbyterian Hospital Dallas and will be available only to the patient, the American Heart Association, Texas Health Presbyterian Hospital Dallas, and the UT Southwestern Institutional Review Board. The storage and processing of all subject information will be consistent with HIPPA regulations.

Potential Benefits

To the individual: Benefits may include improvements in autonomic function and functional capacity associated with exercise training or yoga. Furthermore, a careful history and physical exam with stress-echo may uncover an undetected problem that deserves attention.

To others with similar problems: This study will provide important information regarding the physiology of diastole and the cardiac consequences of visceral adiposity in middle aged adults. It is possible that new information relevant to patients with obesity and diastolic dysfunction may be obtained, and may lead to improved pharmacologic and non-pharmacologic therapies.

To society in general: CHF is a major problem for our aging society and this study holds promise for preventing and treating this disease associated with diastolic dysfunction from a sedentary lifestyle. To date, there are no proven therapies to treat HFpEF and a strategy aimed at preventing the development of disease in high risk patients has tremendous societal benefit.

In assessing the risk benefit ratio for our study, the major benefits include: 1) obtaining meaningful information for society regarding the effects of high intensity exercise training on the cardiometabolic health of individuals at particularly high risk for future development of HF; 2) obtaining important information for the subject regarding ambulatory blood pressure, exercise

performance, cardiac morphology and cardiac function; and 3) providing the subject one year of supervised high intensity exercise training or yoga training, each with associated health benefits. The risks of the study are primarily imposed by exercise training and omega-3 supplementation, both of which carry minimal risk. Hence, in the final analysis, we feel the benefits to both the enrolled individual and to society far outweigh the risks of participation.

Biostatistics

As this study is sponsored by the AHA and passed peer review, the biostatics section is omitted per instructions, but is available in the full protocol. (page 697 of 731 of the AHA grant). Briefly, the primary outcome of interest is reduction in myocardial triglyceride content by MRI spectroscopy. Secondary outcome measures are LV concentric remodeling and diastolic function. The sample size for the study was calculated using a two factor factorial design which provides adequate power to detect a main effect (99%) as well multiple comparisons between individual groups (80%).