Exercise Training in Heart Failure: Structural and Functional Cardiac Remodeling

NCT02275819

09/20/2017

EXERCISE TRAINING IN HEART FAILURE: STRUCTURAL AND FUNCTIONAL CARDIAC REMODELING
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Rational: Prevalence of systolic heart failure (HF) is high among the growing population of older adults[1-3]. Diminished cardiac output limits forward flow, diminishing peripheral perfusion and triggering downstream effects on skeletal muscle health and physical performance. Progressive cardiac remodeling and deteriorating cardiac output have been implicated as key components underlying HF-related exercise intolerance as well as to associated declines in independence and quality of life[1]. ACE inhibitors, beta blockers, and cardiac synchronization all moderate cardiac remodeling and systolic dysfunction, but exercise tolerance as well as high morbidity and mortality persist. Exercise training has been demonstrated to improve longevity and symptoms, even in patients receiving standard neurohormonal and device therapies. Consistently, exercise training benefits have been primarily attributed to training adaptations in the peripheral circulation and skeletal muscle. However, exercise training may also exert cardiac remodeling benefits beyond those of pharmacological and device therapies, with additional systolic and diastolic performance enhancement[4-6].

Statement of the problem Prior studies have looked at the effect of aerobic exercise training benefits on cardiac remodeling in younger HF cohorts. In this study we look at benefits of inspiratory muscle training (IMT) verses aerobic exercise training verses a control in older HF patients. IMT may be particularly more practical and efficacious for an older HF population as it can be used despite physical infirmity and with relatively greater potential to achieve high intensity training goals that achieve the greater systemic physiological effects. Moreover, since we are studying an older HF population in which remodeling has presumably advanced as function of both time and age-related physiological changes, the potential of exercise induced reverse remodeling benefit may be particularly significant.

Specific aims :

Aim 1. To compare the impact of two different types of exercise training (IMT vs. Aerobic training) pre/post on left ventricular structure and function using conventional and novel echocardiographic indices of systolic and diastolic function.

a. We hypothesize that exercise training will result in a decrease in left ventricular end-diastolic and end-systolic volume and increase in ejection fraction as well as regional longitudinal strain (measures of morphology and systolic performance) as compared to the control group.
b. We hypothesize that exercise training will increase mitral annular early diastolic velocity (e') as well as decrease the ratio (E/e') of early mitral inflow velocity (E) and e' (measures of diastolic performance).
c. We hypothesize that both forms of training will be more beneficial compared to the control group and IMT will be non inferior to aerobic training regimen as related to cardiac remodeling.

Aim 2. To explore the association between cardiac remodeling and quantitative exercise training endpoints.

a. We hypothesize that exercise training related central cardiac improvements (indicated in Aim 1) will lead to improved aerobic functional parameters (measured as peak VO_2 and VE/VCO_2 slope)
b. We hypothesize that exercise training-related central cardiac improvements (indicated in Aim 1) will lead to improved quality of life (QoL) and symptom reduction (as measured by questionnaires).

Exploratory Aim: To explore the independent impact of cardiac morphology and pumping parameters on physical function, QoL, and symptom reduction. We hypothesize that when the outcomes of this proposal and the Merit are evaluated in combination that the improvements in cardiac morphology and function will lead to improvements in function, QoL and symptoms independent of peripheral skeletal muscle and vascular dynamics that will be collected as part of the Merit.

Background and Significance

Scope of the problem; high prevalence of HF and relevance of exercise intolerance

Prevalence of Heart Failure (HF) is rising, particularly due to the high incidence of HF among today's expanding population of older adults[1]. Whereas mortality from coronary artery disease, sudden death, and other cardiovascular illnesses has declined, an expanding population is surviving into its senior years when they are paradoxically more susceptible to developing HF [7]. HF prevalence is already over 5 million in the US, and incidence (already 500,000 cases a year) is growing. It is the chief reason adults aged 65 and older are hospitalized, with annual costs exceeding 40 billion dollars a year.

Exercise intolerance is the most frequent complaint expressed by older adult HF patients. Moreover, functional decline compounds overall HF risks with increased mortality as well as increased propensity to

frailty, dependency, and diminished quality of life (QoL)[8]. Multiple studies demonstrate that exercise intolerance is a powerful prognostic indicator of increased mortality and morbidity risks.

Multiple factors potentially underlie exercise intolerance in HF. Central and peripheral mechanisms have been implicated in addition to effects of deconditioning. Exercise training has been shown to decrease symptoms, increase exercise tolerance and lower risk of mortality. However, relatively little is known about the mechanisms (central or peripheral) underlying exercise induced benefits.

This proposal evaluates the affects of different modalities of exercise training on cardiac remodeling and related differences in ventricular systolic and diastolic remodeling and performance. This study complements the already funded proposal VA Merit F0834-R entitled "Exercise Therapy to Reduce Heart Failure Symptoms; Sorting Mechanisms of Benefit" Exercise Therapy) Site-Principal Investigator [PI], Gottlieb; Prime-PI Formanthat is focused primarily on peripheral mechanisms of exercise intolerance in older patients with HF, and the related benefits of exercise training on skeletal muscle gene expression.

This proposed study on cardiac remodeling will compare the effects of aerobic training to inspiratory muscle training (IMT) to delineate relative training differences. IMT is a novel training method that may be tolerated better among older HF patients, particularly because many of these patients are prone to infirmities that impede their capacity to undertake and/or advance intensity of aerobic exercise. IMT may facilitate exercise and exercise progression in patients for whom it might otherwise not be feasible. Although clinical benefits of IMT are apparent in patients with HF, the specific benefits of IMT on cardiac remodeling have never been assessed.

HF progression and cardiac remodeling

Cardiac remodeling can be defined as a process that results in alteration in the ventricular architecture, with associated change in ventricular volume, as well as altered chamber size, shape and function in response to cardiac injury. At the cellular level, this is associated with myocyte hypertrophy, myocyte apoptosis, myofibroblast proliferation and interstitial fibrosis[9]. Although remodeling was initially described in association with myocardial infarction (MI)[10], it was subsequently demonstrated to be common in HF of multiple etiologies, with comparable effects on progressive clinical risk and deterioration[9,11,12].

Cardiac remodeling typically starts as a physiologic compensatory process in response to myocardial necrosis (as in acute MI), myocarditis, idiopathic dilated cardiomyopathy, pressure overload (associated with aortic stenosis and hypertension) or volume overload (associated with valvular regurgitation). Although the etiologies are different, common pathways at the cellular level underlie progression of the disease and induce transition from stable disease to HF as the process ultimately becomes maladaptive[9,13-16].

In HF, remodeling leads to changes in the geometry of the heart. It becomes more spherical, with mounting ventricular mass and volume that increase wall stress and lead to progressive ventricular dysfunction. At the cellular level there is myocyte hypertrophy, necrosis, apoptosis, fibrosis, increased fibrillar collagen and fibroblast proliferation[9,13-16].

There are several factors influencing this process of remodeling including hemodynamic load and neurohormonal activation. Neurohormonal activation in HF which starts as a compensatory mechanism due to falling cardiac output plays a major role in remodeling and disease progression by activating the renin angiotensin aldosterone system (RAAS) and sympathetic nervous system which stimulate collagen synthesis. Other factors influencing remodeling include increased oxidative stress, pro-inflammatory cytokines (TNF-alpha and interleukins) as well as endothelin[9,13-16].

Well known therapeutic interventions in HF such as RAAS inhibition and B-adrenergic blockade have targeted HF remodeling pathophysiology resulting in reverse remodeling and significant improvement in morbidity and mortality[5,6,9,17-25]. Reverse remodeling is also thought to be the major mechanism underlying benefits of device therapies, chronic resynchronization (CRT) and left ventricular assist devices (LVAD)[13]. Furthermore, new pharmacologic agents to reverse remodeling continue to be developed, including medications to prevent or reverse inflammation, alter the collagen matrix and forestall cardiomyocyte death[14].

While most of the life-prolonging advances in HF management have been attributed to therapies that reverse maladaptive remodeling, the functional gains achieved by these therapies have been equivocal. Many have therefore assumed that residual functional limitations are mediated primarily by peripheral mechanisms. However, it is also plausible that remodeling and related physiological benefits may not have been optimized. Notably, reverse remodeling has usually been assessed in terms of the associated benefits on systolic function. In this study, in addition to assessing the effects of exercise training on systolic function, we assess

utility of exercise training to induce reverse remodeling effects on diastolic function among HF patients. Optimization of diastole may confer a more significant increase in functional capacity and other healthful benefits.

Exercise training induced benefits on the central circulation

There is significant published data in patients with HF demonstrating exercise-induced improvement in functional capacity, symptoms and quality of life. However the mechanism of this benefit is still being evaluated. Response to exercise is complex and involves a close interplay between the central circulation, ventilatory system, peripheral vessels, and skeletal musculature[26].

Relevant physiology for exercise induced cardiac remodeling:

In young healthy individuals cardiac output may increase 5-6 folds during maximal exercise. Increased heart rate with exercise is responsible for majority of the increase in the cardiac output. Maximal heart rate varies among individuals and does not increase with exercise training. However stroke volume both at rest and exercise increases significantly with prolonged exercise training. Cardiac chamber enlargement and the ability to generate a large stroke volume are well known direct results of exercise training[27].

Changes in cardiac output as well as peripheral vascular resistance (PVR) are distinctly different in different forms of training. For example isotonic exercise or endurance exercise is associated with sustained elevations in cardiac output and normal or reduced PVR. On the other hand isometric exercise or strength training activity is characterized by increased PVR and normal or only slightly elevated cardiac output. This increase in PVR causes transient marked elevations in systolic pressure and afterload [27].

Effects of Exercise training in cardiac remodeling and function:

The role of exercise training in cardiac remodeling and function has been extensively studied in healthy and diseased populations. In normal trained athletes early 2-dimensional echocardiographic studies documented left ventricular (LV) hypertrophy and dilation. Subsequent studies in elite Italian athletes reported increased wall thickness in association with increased chamber size[36]. It was soon recognized that morpholgical changes induced by exercise are also distinctly different in different forms of training. Strength training is associated with concentric hypertrophy where as endurance training is associated with eccentric LV enlargement[29].

Impact of exercise on LV function with resting echocardiograophic ejection fraction has been studied in numerous studies[36]. It is noted that healthy endurance athletes may demonstrate normal to mildly decreased EF. Strength training however is associated with normal to hyperdynamic resting left ventricular ejection fraction (LVEF). Studies with regional LV mechanics have revealed increase in LV radial and longitudinal strain as well as increase in LV torsion and LV early diastolic untwisting rate[,28,30,33].

Effects of Exercise training on systole in HF:

Effect of different forms of exercise in stable HF patients has been studied in a number of trials. In one meta-analysis[31] that included 14 trials reporting LVEF data (n=812), 7 trials reporting end-diastolic volume (EDV) and end-systolic volume (ESV) (n=569), aerobic training significantly improved LVEF (9 trials, n=538), EDV (n=371) and ESV (n=371). However combined aerobic and strength training was not associated with significant improvement in LVEF, EDV or ESV.

Another meta-analysis by Haykowsky et al.[35] studied the effect of high intensity aerobic interval training as compared to moderate –intensity continuous aerobic training and found that although peak oxygen uptake (VO_2) improved with high intensity interval training, LVEF was not different.

Chen and colleagues[32] in another meta-analysis published last year studied anti-remodeling benefit of exercise training by assessing EF, EDV and ESV and included 15 randomized controlled trials with 813 patients. They found that aerobic exercise improved LVEF, EDV and ESV. Subgroup analysis with exercise duration however indicated that the positive effect was noted only in the group with more than 6 months of training and no benefit was noted in the group with short term exercise. Most importantly strength training either alone or in combination with aerobic training was not associated with improved remodeling.

Effects of Exercise training on Diastole in HF:

Relatively fewer studies have evaluated the role of exercise training on diastolic function in HF patients[5,20]. These studies have demonstrated significant improvement in diastolic function with exercise training (increase in E wave and E/A ratio, decrease in deceleration time, increase in e' and decrease in E/e' ratio). Sandri and his colleagues[5] studied the response of diastolic dysfunction to endurance training in 60 HF patients compared to reference controls who were randomized to 4 weeks of supervised endurance training and found that LV

isovolumic relaxation time decreased by 29% in young and 26 % in old (>65 years) HF patients. Septal e' increased by 37% among young and 39% among old HF patients with resulting significant Decrease in E/e' ratio. In association with this there was significant reduction in serum levels of N-terminal pro brain naturetic peptide. This prospective randomized study illustrates the fact that exercise training is highly effective in improving diastolic function in HF patients irrespective of age.

In summary, all of the studies noted above again highlight the fact that the effect of exercise on cardiac remodeling and function can be quite variable depending on the type of exercise and the duration of exercise thus emphasizing the fact that every new form of exercise has to be formally studied for its beneficial effect on cardiac remodeling before implementing it for clinical purpose (as we are planning with IMT in our proposal)

Exercise Training: unique rationales to different training modalities

- *Aerobic training:* Exercise training for HF was once predominantly oriented towards aerobic training modalities; building on the rationale that aerobic exercise stimulates healthful central cardiac responses[3,26,63] in adults without heart disease. Aerobic training has the potential to induce increased stroke volume and inotropy in healthy adults, as well as increased peripheral oxygen utilization. Several randomized studies have reported the effect of aerobic training in HF and demonstrated improved ventricular structure (fall in left ventricular volumes and linear dimensions) and systolic function (improvement in LVEF) with training[4,17,18,34,38-40].
- *Inspiratory Muscle Training:* HF patients have also been demonstrated to have reduced inspiratory muscle strength and endurance that exacerbates dyspnea[38] and exercise intolerance. Inspiratory muscle strength correlates with VO_2 in HF and is an independent predictor of survival[39,40]. IMT has been demonstrated to improve the respiratory muscle metaboreflex as well as many of the pathophysiologic manifestations of HF. Quality of life, heart rate, respiratory rate, peak VO_2, 6 minute walking distance, minute ventilation (VE), breathing efficiency (the VE/VCO_2 slope) and oxygen uptake efficiency slope (OUES), and recovery oxygen kinetics have all been shown to significantly improve after IMT in HF patients[41-51]. In one study Dall'Ago et al showed maximal inspiratory pressure increased 115% in the IMT group with 17% improvement in peak VO_2 and 19% improvement in 6MWT distance[42]. However within this literature, there is no research indicating the impact of IMT training on central mechanisms (cardiac reverse remodeling and/or changes in systolic/diastolic function). It should be noted the current proposal intentionally excludes patients with HF with preserved ejection fraction (HFpEF) as the clinical utility of IMT for HFpEF have not been established, and studying cardiac remodeling with IMT in this group is premature.

In summary this proposal evaluates central cardiac changes with exercise training in HF patients. Furthermore, it adds to the literature by comparing two training modes (IMT and aerobic training) verses controls. IMT is a novel exercise regimen that facilitates high intensity training of the diaphragm. Prior research has demonstrated systemic benefits akin to more traditional exercise training. In this study we will compare IMT to standard aerobic training to assess clinical benefits, but even more importantly on remodeling, diastole and systole, and the relative differences on central and peripheral mechanisms of disease. We expect IMT to be non-inferior compared to aerobic training in its benefits and in addition will have certain advantages over traditional aerobic training because it will not be restricted by notorious musculoskeletal limitations that so frequently encumber exercise-training goals in HF patients, who are typically old, deconditioned and limited by other morbidities and pain.

Furthermore, the combination of the proposed study with the funded Merit trial (which is primarily focused on peripheral aspects of HF pathophysiology in relation to exercise training) will provide comprehensive assessment of remodeling in relation to peripheral training effects (i.e., skeletal muscle gene expression, fiber types, and muscle perfusion) and the interplay between them. This study also offers the unique opportunity of studying the effect of exercise training on both systolic and diastolic function in the same group of HF patients, which to our knowledge has not been done in any randomized study before.

PRELIMINARY DATA

Dr. Aragam is a clinical research echocardiographer and has served as the director of two large echocardiography laboratories. At Massachusetts General Hospital she was involved in experimental research in echocardiography and worked on Color Doppler Assessment of epicardial coronary arteries in both in vivo and in vitro flow models[52]. Dr. Aragam is currently playing a lead role in multiple approved VA research grants in which her lab will be responsible for key assessments of left and right ventricular function. She recently completed a study showing that functional MR was associated with increased incidence of combined end point of increased hospitalization as well as death compared to patients without significant MR[37].

In work with the Framingham Heart Study (FHS), Dr. Aragam worked in several projects[55,56] focused on longitudinal remodeling of the left ventricle and left atrium and the associated clinical correlates. One of these investigations entailed serial echocardiographic observations over a sixteen-year period in 4062 FHS participants (mean age 45 years, 54% women; 11,485 person-observations). It was noted that cardiac remodeling over the adult life course is characterized by a distinct pattern of increasing LV wall thickness, decreasing LV dimensions, and increasing fractional shortening with advancing age. Overall, female sex, greater blood pressure load, and presence of diabetes mellitus served to attenuate the remodeling pattern. These observations suggest a mechanism for the preponderance of women with hypertension and individuals with diabetes among patients with diastolic heart failure[53].

In another FHS study she studied 4403 participants (mean age, 45 years; 2% women). Age, sex, body mass index (BMI), systolic and diastolic blood pressure (BP), diabetes, and antihypertensive treatment were correlated to left atrial dilation (LAD). This longitudinal study identified higher BP and greater BMI as key modifiable correlates of LAD, suggesting that maintaining optimal levels of these risk factors through the life course may prevent atrial remodeling and AF[54].

Dr. Aurigemma is one of the leading experts in the field of heart failure with preserved ejection fraction (HFpEF) particularly as it relates to cardiac imaging. He has a longstanding interest in cardiac remodeling and function in patients with pressure induced hypertrophy due to hypertension, aortic stenosis, and heart failure. Much of his work has focused on the use of novel indices of systolic function in patients with pressure overload hypertrophy and valvular heart disease. More recently he has shifted his attention to the issue of cardiac remodeling in obesity and in the peculiar phenomenon of stress cardiomyopathy, a disorder which shares many features with the type of acute cardiac remodeling seen in ischemic injury to the myocardium. He is an expert in all of the standard indices of systolic and diastolic function which will be used in the proposed analyses, as well as the more novel indices, such as strain imaging and midwall shortening. He has contributed pioneering work in the field of strain imaging[57-59].

Dr. Baggish, is also an internationally recognized expert in echocardiographic imaging with a focus on measuring changes in cardiovascular structure and function in response to exercise training in healthy subjects and competitive athletes[27]. He has designed and completed numerous longitudinal studies examining changes in cardiac structure and function in the settings of exercise and hemodynamic perturbations[81-84]. Specifically, he has employed longitudinal, repeated measure studies to assess the response of the heart to vigorous physical exercise[28,62,85-86]. In this setting, he has helped to define the right and left ventricular responses to aerobic and static exercise using both conventional and more advanced echocardiographic parameters. His group has published sentinel works using echocardiographic derived strain, strain rate, and ventricular torsion in the setting of volitional human exercise[28,33]. This body of work has helped to define the expected response of the myocardium to moderate and high intensity exercise training. It is anticipated that the experience of both Drs. Aurigemma and Baggish will complement the stated goals of the current proposal.

Dr. Forman has completed prior work in exercise training, exercise testing, and peripheral mechanisms for HF patients. He is well-oriented to address cardiovascular issues in relation to the impact on physical function. His VA Merit Award, *Ubiquitin Proteolysis and PGC-1α in Skeletal Muscle (SkM) in HF* provided the perspective and rationale for the subsequent VA Merit F0834-R entitled “Exercise Therapy to Reduce Heart Failure Symptoms; Sorting Mechanisms of Benefit” (PI, Forman) to which this proposal is complementary. In the initial study, aerobic and strength parameters were diminished in HF vs. controls. Expression of key proteolytic genes (e.g., FoxO1 and Fo

xO3) was increased in SkM in HF vs. controls[60]. Surprisingly, expression of the anabolic gene PGC-1α suggesting an important counter-regulatory mechanism to preserve function (in submission).

Dr. Forman also has an extensive experience in HF training studies, including the NHLBI aerobic training trial HF-ACTION and the NECOM tai chi training trail[63,64]. He is highly sophisticated in the training required for this investigation but most of his research has focused on exercise training-related differences physical function, SkM physiology and mortality benefits rather than cardiac remodeling or cardiac functional changes. In one trial of older female HFrEF patients, those randomized to a 10-week strength training program had significantly increased SkM (43.4±8.8% vs.-1.7± 2.8% in controls, p= 0.001) and endurance (299±66% vs. 1±3%, p= 0.001). Citrate synthase improved significantly 35±21%[61].

Dr. Bhatt is an international leader in clinical trials. Among his impressive list of achievements, he was PI for the CHARISMA trial which compared clopidogrel plus aspirin with aspirin alone in stable atherothrombosis.

He served as the co-chair of the CHAMPION-PLATFORM, CHAMPION-PCI, and CHAMPION-PLATFORM studies, among the largest trials of a pharmacological agent ever performed in the field of interventional cardiology. He is also chair of the COGENT study, which was the first trial to demonstrate that proton pump inhibition reduces clinical gastrointestinal bleeding when given prophylactically to patients on dual antiplatelet therapy. Dr Bhatt's organizational clout and reputation will help garner the substantial investment and priority that the VA Section of Cardiology will accord this research study. The trial will be well promoted and organized with the help of Dr. Bhatt's hands-on approach and commitment.

Materials and Method

In a two year randomized, pilot study, two exercise training regimens (IMT and Aerobic) will be evaluated as compared to a control group by studying their effect on clinical end points and correlating them with central effects on cardiac remodeling specifically focusing on indices of left ventricular systolic and diastolic function (LVEDV, LVESV, EF, LV mass, LV longitudinal strain e' and E/e). Given that prior studies have predominantly studied aerobic exercise and there is no data available on the effect of IMT on cardiac remodeling or the peripheral effects, this study will provide us the unique opportunity to study IMT to determine its efficacy compared to aerobic training and will also provide mechanistic insight to overall change in symptoms. We anticipate that insights from this work will facilitate clinical implementation of exercise training and potentially provide insight into the use IMT as a therapy in individuals with HF who cannot perform aerobic exercise.

Overall Study Protocol: 75 HF patients will be enrolled. HF diagnosis will depend on physician diagnosis[65-68]. As part of this protocol 15 control subject will undergo a comprehensive pre- and post- assessments that will include a battery of physical function evaluations (aerobic, strength, and questionnaire indices), quality of life (QoL), and echocardiography. At the conclusion of their initial assessments they will continue with usual clinical care and will be retest on the same battery of assessment 12 weeks later. 60 patients already taking part in the VA MERIT F0834-R will have the option to additionally enroll into this study which would require them after enrollment into the Exercise Therapy protocol to complete an echocardiogram at baseline as well as post-intervention. All other parts of their participation will occur as part of the Exercise Therapy trial.

Table 4: Outline of protocol (by visit) for Controls group

Initial Assessment	Visit 1	Informed consent and physical exam, physical functional assessment battery (aerobic, strength, 6MWT, Hand Grip, and questionnaires), and echocardiographic
Exercise Training	12 weeks	Care as usual
Post assessment	Visit 38	Post-exercise assessment battery will mirror visit 1

Table 5: Outline of protocol (by visit) for Intervention Group

At time of randomization from VA MERIT F0834-R visit 3 of that protocol	Initial Assessmen	Visit 1	Informed consent and echocardiographic
As part of the VA MERIT F0834-R	Exercise Training	12 weeks	2-3 times a week of exercise training
At time of the third visit for VA MERIT F0834-R	Post assessment		echocardiographic

Recruitment

- *Study Population:* 75 male and female HF patients with mild-moderate symptoms while on optimal medical therapy will be enrolled. The data collected from this pilot study will be used for building future research. HF diagnosis will be contingent on a previous hospitalization for HF or physician assessment of HFassociated with either systolic or diastolic dysfunction, or on left ventricular ejection fraction ≤45% in the absence of a physician diagnosis of HF (i.e., AHA stage B heart failure). Each candidate will be examined at the time of enrollment by a physician and/or cardiologist to ensure that he/she is clinically stable.

Inclusion Criteria: (a) NYHA class II or III or AHA Stage B or C with reduced ejection fraction (≤45%), or AHA Stage C HF with preserved ejection fraction despite a minimum of 6 weeks of optimal treatment. (b) Age ≥50 years. (c) Optimal therapy according to AHA/ACC and HFSA HF guidelines, including treatment with an ACE

Inhibitor (or an angiotensin receptor blocker) and beta-blocker therapy (for at least 6 weeks), or have documented reason for variation, including medication intolerance, contraindication, patient preference, or personal physician's judgment.

Exclusion Criteria: (a) Major cardiovascular event or procedure within the prior 6 weeks. (b) Dementia. (c) Severe COPD (FEV1<50%), PVD that would limit exercise. (d) End-stage malignancy. (e) HF secondary to significant uncorrected primary valvular heart disease (except mitral regurgitation secondary to LV dysfunction and asymptomatic aortic regurgitation) (g) Orthopedic exercise limitation. (h) Women who are pregnant, breastfeeding, or likely to become pregnant within the next 6 months. (i) Psychiatric hospitialization within the last 3 months. (i) valve replacement or repair in past 12 months, (k) Chronic ETOH or drug dependency.

Recruitment for this pilot project will primarily draw from the larger funded Exercise Therapy which is currently enrolling patients.. Once participants have completed the initial baseline visit for the Exercise Therapy study they will be told of this additional study and will be provided the option to participate if they chose to. If they chose to participate they will complete an echocardiogram prior to starting the exercise intervention as part of the Exercise Therapy protocol.

In addition control participants will be recruited though posted flyers (at all VABHS campus), mailings, and in clinic recruitment. In clinic recruitment will occur at the West Roxbury campus at the Heart Failure clinic. Dr. Joseph is Director of the VA Heart Failure Program, a highly successful clinical program with over 500 HF patients, and a strong track record of recruitment into clinical trials. Dr. Joseph works with two physician, two nurse practitioners, and two fellows to manage patients in this program, and they have established a track record of working together to identify HF patients who can be invited to participate in trials (consistent with HIPAA guidelines). Moreover, Dr. Joseph has also organized a comprehensive HF list of patients attached to the HF program over the past 8 years; this has helped grow recruitment efficacy for mailings to potentially eligible patients, and is a recruitment asset that will be used for the proposed trial.

Echocardiographic Assessment: All echocardiographic assessments will be performed at the West Roxbury VABHS campus where Dr. Aragam is the Director of the Echo Lab. All subjects will have comprehensive echocardiographic studies in which all traditional echocardiographic parameters will be assessed, including comprehensive assessment of LV/RV structure and both systolic and diastolic function as recommended by the American Society of Echocardiography guidelines[72,80]. Left ventricular end diastolic and end systolic volumes and ejection fraction (EF) will be measured by 2D (modified Simpson's method)[72] as well as 3D TTE using an X5 probe and an offline analysis with Q-lab software (Phillips Burlington) [88] LV mass will be measured by the area length method[72]. For systolic assessments, in addition to traditional indices of LV volumes and EF, novel parameters, including longitudinal strain, strain rate, and LV twist will be measured[55,87]. Diastolic function assessments will include traditional measures of mitral inflow velocity (E), mitral annular tissue velocity (E'), ratio of E/E', mitral flow propagation velocity as well as isovolumic relaxation time (IVRT) pulmonary venous flow profiles, and LV untwisting rate[71,87.] Indices will also include measurement of left and right ventricular wall thickness, cavity dimensions, LA volume, right ventricular systolic function, cardiac output as well as pulmonary pressure. Please see appendix 2 for imaging protocol.

Functional Assessments and Exercise Training: Exercise assessments and exercise training for particpants taking part in the intervention portion of the proposed study will be based off of and completed as part of the funded VA MERIT F0834-R to which this study is complements. For those that will be controls for the proposed study their assessment will be completed independent of the funded Merit. Functional assessments and training sessions will be completed at the JP VABHS.

The battery of physical function assessments will include aerobic, strength, inspiratory, and questionnaire indices to provide a comprehensive assessment of performance at baseline, after training.

- *Cardiopulmonary Exercise (CPX) Testing:* Treadmill exercise testing in association with air-gas-exchange, generally considered to be an optimal gauge of aerobic capacity[73]. A motor-driven treadmill (Woodway) will be used to generate the exercise stimulus. A modified Naughton protocol will be utilized. A lightweight disposable pneumotach device will be positioned in the enrollee's mouth during the exercise for gas exchange assessments (MedGraphics Ultima). Peak VO_2, VAT, the VE/VCO_2 slope, and respiratory exchange ratio (RER), as well as hemodynamics (max heart rate [HR] and blood pressure [BP]), time, and ECG waveforms).
- *B*oth the Borg Rate of Perceived Exertion (RPE)[74]and the Modified Borg Scale for Perceived Dyspnea (Shortness of Breath) will be completed during the CPX and the 6MWT to assess symptoms.

- *Six Minute Walk Test (6MWT):* The 6MWT is also a commonly used assessment of aerobic capacity and submaximal endurance in HF patients. As a measure of everyday walking activity, it is often felt to complement the insights afforded by CPX indices. Using methodology described by the American Thoracic Society[75].
- *Hand Grip Strength:* Hand grip strength is commonly used as an assessment of upper body strength, and is also an important factor in activities of daily living. The maximum force attained will be used.
- *Test of Incremental Respiratory Endurance (TIRE):* TIRE is a measure of respiratory performance. It is achieved by using a specialized pneumotach-type device (RT2; DeVilbiss Healthcare Ltd) connected in series with a laptop or desktop computer [47,49]. Inspiratory muscle strength is measured as the maximum inspiratory pressure (MIP) at residual volume (RV). Single breath inspiratory work capacity will be measured as SMIP and will be measured from RV to total lung capacity (TLC). Total inspiratory muscle work achieved during a testing or training session will be measured as accumulated SMIP (ΣSMIP) at 40% of SMIP, and will be the primary measurement of inspiratory muscle endurance.
- *Quality of Life and Functional Assessment Questionnaires*:
  - ✓ The Duke Activity Status Index (DASI)[76] is a 12-item scale that has been validated in cardiac patients against peak VO_2, and has been demonstrated to be a reliable and responsive tool to quantify physical activity in daily living.
  - ✓ The Kansas City Cardiomyopathy Questionnaire[77] will be used to measure disease-specific health-related quality of life (QOL).

Those individuals that are in the "intervention group" will also be taking part in the research study "Exercise Therapy". As part of the "Exercise Therapy" study they will be randomly assigned to one of two exercise interventions (aerobic or Inspiratory muscle training). The differences between outcomes of these two groups will be evaluated in relation to changes within the echocardiogram as part of this study, however the exercise interventions are taking place as part of the Exercise Therapy study for the exercise is detailed below.

Exercise Training: Both aerobic and inspiratory muscle exercise regimens will total 60 minutes in length and will be scheduled 2-3x weekly for 12 weeks. This volume of exercise has consistently been shown to significantly improve functional performance and physiologic measures of interest in HF patients[3,50,78]. Each exercise regimen will be designed to achieve a similar volume of exercise and to also achieve equivalent social/support dynamics of group training (camaraderie, encouragement). If training sessions are missed, exercise intensity will initially be reduced (using RPE at 13-14 to guide the stimulus) when subjects return, and intensity will then re-advanced over the next 2-3 sessions to make-up for any declines.

Prior to and immediately following all exercise trainings group, a 5-minute warm-up and a 5-minute cool-down period will occur. All participants will under the same the warm-up and cool-down phases during which they will perform slow aerobic (less than 30% of their maximum) and stretching. The warm-ups and cool downs will be matched between groups to ensure that changes seen between groups in outcomes is directly from the exercise type not from any difference format.

- *Training Regimen #1: Aerobic Exercise Training:* sessions will be 2-3x/week for 60 minutes, and will encompass 45 minutes of continuous aerobic exercise proceeded and followed by warm-up, cool-down, and stretching for a total of 60 minutes of exercise time. The intensity of endurance training can range from 40 to 80% of baseline exercise capacity depending on the fitness of an individual. Lower intensity (30 to 40%) regimens may constitute an adequate training stimulus for sedentary adults and/or those who are older or frail. However, for most adults, training intensities of 55 to 80% of the baseline exercise capacity are well tolerated and safe, and lead to relatively more substantial improvements in cardiovascular fitness and health. The Borg scale (rate of perceived exertion index) from 6 to 20 will be used to help guide exercise from moderate to high training intensity (12 to 16) over the course of the trial. The goal of the aerobic exercise will be for patients to achieve 45 minutes of continuous aerobic exercise. However, for patients who cannot sustain this exercise duration, shorter intervals will be used (e.g., exercise then rest then exercise, using 10 minute bouts of exercise followed by short rest), that progressively elongate over time (as tolerated). Additionally the intensity will be progressed over time as tolerated, i.e., starting at 40% and then working up to 80% over time.

- *Training Regimen #2: Inspiratory Muscle Training:* sessions will be 2-3x/week for 60 minutes, and will encompass 45 minutes of IMT proceeded and followed by warm-up, cool-down and stretching for a total of 60 minutes of exercise time. Two different methods will be integrated: TIRE and Threshold IMT. Subjects will wear a noseclip during both forms of IMT. TIRE IMT provides both power and endurance IMT. Threshold IMT provides only endurance IMT.

TIRE IMT will be administered progressively 40% week 1, 50% week 2, 60% the remainder of the protocol of the Maximal Inspiratory Pressure (MIP) and SMIP using a visual target that the patient watches on a monitor during the training. The visual target has been observed to facilitate inspiratory performance via biofeedback while the IMT progresses in respect to the work to rest ratio, with rest periods decreasing from 60 seconds at level A to 45, 30, 15, 10 and 10 seconds at levels B through F, respectively. TIRE IMT is characterized by through-range IMT with the need for patients to match or exceed 90% of the desired percentage of the on-screen target throughout the entire inspiratory effort (from RV to TLC). Thus**,** the training session continues until task failure indicated by an inability to match 90% of the on screen target, or until a maximum of 36 resisted breaths have been performed with an average duration of 25 minutes[43,46]. Adherence and performance during TIRE training is captured automatically via TIRE computer software and each session is automatically performed at the desired workload (40% of MIP). An additional 20 minutes of IMT will be completed using the Threshold IMT. Threshold IMT will also be administered at progressively (40%, 50%%, 60%) of MIP which will be adjusted each week to maintain a workload at 60% of MIP. Threshold IMT will require subjects to breathe through the mouthpiece of the Threshold device at a comfortable rate using diaphragmatic breathing techniques.

While prior studies have used a variety of training intervals and exercise intensities to achieve physiological benefits, in this protocol, we opted for a standardized 2-3x/week, 60 minute, 12 week regimen which is the best studied and validated training frequency and duration in which to achieve efficacy[3, 40-43,48,78].

Subject Retention: Utility of exercise will be emphasized to each exercise block throughout the course of the trial. If patients miss sessions, they will be immediately telephoned. A letter will be used to reach those who do not show for two or more sessions. As noted, exercise will be modified upon a patient's return from any missed sessions, but since exercise training is being administered on an intention to treat basis, the sessions will not be "made-up." Every effort will be made to foster a mutually supportive group dynamic, with the hope and intention to build expectations among the participants to support and encourage one another.

Project Time Line

Year I →→→→	Year II →→→→
Start Recruiting	Continue Recruiting
Start Assessments	Assessments
Start EX sessions	Exercice Sessions
	Manuscript Preparation

Year	Year 1		Year 2	
Time frame	0-6M	6-12M	12-18M	18-24M
Staffing	ES, RA, EX	ES, RA, EX	ES, RA, EX	ES, RA, EX
Enrollment	15	20	20	10
What will be happening	Setup/purchase supplies/ recruitment/ initial assessment /	Recruitment/ assessments/ interventions	Recruitment/ Assessments/ interventions	Recruitment/ Assessments/ interventions / manuscripts preparation

Study Team: Throughout the trial, Dr. Aragam will meet regularly with co-investigators (4 times a year initially, and increasing to monthly when data analysis begins). Drs. Forman, Gottlieb, Joseph, Bhatt, Gagnon, Baggish all work in the VA or within close proximity and can presumably come to the VA campus for these meetings. However, phone teleconferencing will also be available for those who cannot participate in person. The skillsets and backgrounds of the investigators (as detailed in their biosketchs and the budget section) are extremely complementary and have contributed to a collegial and productive dynamic.

All study staff that will be working on this project are currently on staff at the VABHS. The echo sonographer, research assistant, and exercise physiologist will be an integral part of the team, they will coordinate recruitment, participant screening, enrollment, perform assessment visits, and follow ups. The current VABHS infrastructure through the Clinical Studies Unit (CSU) provide the ability for one exercise physiologist to perform the functional assessment while another performed the exercise trainings. This will allow this physiologist to remain blinded to the subject's intervention group thus eliminating tester bias.

Statistical Analysis: *General considerations:* This is a pilot study, described below are continuous outcome measures, primarily changes in function outcomes and gene expression and either continuous or categorical predictors. In all instances, outcome variables will be evaluated for violation of model assumptions and transformation of these variables will be considered as a remedy if needed. Analyses will generally be performed with an intent-to-treat approach, with sensitivity analyses performed to assess the role of drop-outs on the results.

Randomization will be generated using a SAS program based upon permuted random blocks of variable size to assure approximate balance over time and will be stratified by sex and statin use.

Aim 1a: ***a)*** *We hypothesize that exercise training will result in a decrease in Left ventricular end diastolic and end systolic volume and increase in ejection fraction (measures of morphology and systolic performance) as compared to the control group.* ***b)*** *We hypothesize that exercise training will increase mitral annular early diastolic velocity (e') as well as decrease the ratio (E/e') of early mitral inflow velocity (E) and e'(measures of diastolic performance.* ***c)*** *We hypothesize that both forms of training will be more beneficial compared to the control group and IMT will be non inferior to aerobic training regimen as related to cardiac remodeling.*

The outcomes for these hypotheses will be the outcome measures at baseline and at the end of follow-up. Parts a & b involve superiority tests using a mixed linear regression model comparing each active treatment group to the control group, specifically the interaction between time and treatment, with the ability to adjust for baseline values of the outcomes. Part c requires a test of non-inferiority between the two active treatments also involving a mixed model with a lower bound of 0.65 standard deviation units for each measure [see Sample Size and Power below].

Aim 2. *To explore the benefits of improved cardiac remodeling and physiology on functional and qualitative exercise training endpoints.* ***a)*** *We hypothesize that exercise training related cardiac improvements will lead to improved aerobic functional parameters (measured as peak VO_2 and VE/VCO_2 slope).* ***b)*** *We hypothesize that exercise training-related cardiac improvements will lead to improved quality of life.*

For hypotheses a & b, baseline and follow-up in peak VO2, VE/VCO2 slope and quality of life will be the outcomes in separate mixed linear regression models using the measures of morphology, systolic and diastolic *performance* at evaluation times that were used as outcomes in aim 1 as predictors.

Exploratory Aim. Using the outcomes form aim 2 in separate mixed linear regression models using the predictors from aim 1 with the addition of potential confounders of peripheral function as determined by the supporting funded Merit to. We will evaluate the independent effect of central cardiac change on function.

Sample Size and Power: With respect to superiority testing for mixed models in **aim 1,** power for an equivalent t-test will be used with sample sizes of 30 for the active treatment and 15 in the control group. This will result in the ability to detect a difference of 0.91 standard deviation [SD] units with 80% power, assuming an alpha level of 5%. For non-inferiority testing in aim 1, we propose a detectable difference of zero, with a lower boundary of 0.65 SD units, which provides 80% power using an alpha level of 5%[79].

In **aim 2,** a mixed linear regression model with 7 predictors would result in a detectable R^2 of 0.19 compared to a null model with 80% power, assuming alpha=5% and 75 subjects.

Study Data Management and Quality Control:

Prior to the initiation of the study, all investigators and research staff involved in clinical activities will meet to review study procedures and will complete all required trainings on data and patient privacy procedures. Documentation of any protocol breaches will be required. Each protocol violation will be evaluated by the PI and a determination made regarding the validity of any justification for the violation.

The study databases will be located at the VABHS. The clinical database with all research data will be stored on VA network drives and housed behind the VA firewall on VA owned and maintained servers, which are backed up on a regular schedule. All computers will have Kerberos passwords and come equipped with antivirus software. Data will not be stored on desktops or on non-VA servers. Study data will be coded with a unique study identifier for each participant and stored in a de-identified manner. A study data set without identifiable information will be used for all data analysis. Identifiable information will be collected for patient tracking and safety purposes, but will only be kept for as long as the study is active. De-identified clinical data will be stored separately from the participant's name, contact information, and real SSN. Access to the cross-walk file linking the participant's identifiers and their study data will be restricted to the project manager. This file will be destroyed according to CSP policy after the study ends. Study data will be retained and stored after the study ends according to federal and local VA regulations. Access to the study data is heavily restricted to

individuals with approval from the PI to access the data. Individuals must be properly credentialed research staff and must be compliant with VA security trainings (i.e., Research Data Security, HIPAA and VA Privacy Training, Cyber-Security, and Good Clinical Practices).

Dissemination and/or Implementation Plan: The findings of this study will be of key interest in a variety of scientific and clinical venues. Abstracts and associated manuscripts will target the Echocardiography, HF, and exercise research communities. Initial presentations/publications will include orientation to cardiac remodeling effects with focus on the overall mechanism of exercise induced clinical benefits and the relative contribution of central and peripheral effects with the 2 training modalities We will also report on the role if exercise training modalities and their impact on heart failure management, issues of likely interest to HF and cardiac rehabilitation physicians. Dr. Aragam and her team of investigators will participate in related meetings, particularly the American Heart Association (AHA). Drs. Aragam, Forman, and Joseph already regularly participate in the AHA/ACC/ASE as part of their careers. Likewise, the investigators participate in the American College of Sports Medicine, the HF Society of America and other laudable venues as part of their careers. Dissemination of the data/conclusions from this study will flow from these preexisting patterns.

Limitations: The goal to recruit 75 systolic HF patients, inclusive of men, women, and minorities is an inherent challenge for a two year proposal. We are confident we can achieve this because of the significant and well-organized initiatives we established within the VABHS (as part of previous pilot studies) to identify suitable candidates. A related limitation is the potential attrition of patients over an extended training trial. Illness and/or life stresses can potentially exacerbate attrition. Dr. Forman developed considerable experience with these types of dynamics in HF-ACTION (a large training trial in which there was only 5% attrition), and he will work closely with the study team to maintain subjects' adherence. Financial incentives will be helpful, but it became clear in HF-ACTION that the PI was the most important factor in maintaining patient participation. Steps will also be implemented to sustain participation in the event of illness, accidents, or travel.

Patients can also dilute the training effects if they modify their regimen by doing supplemental exercises at home (e.g., adding aerobic exercises by those in the IMT arm of the study). We will emphasize the priority of maintaining precise training regimens, and will offer patients the chance to cross-train as soon as the formal protocol is completed.

Although the current proposal employs well-validated exercise training parameters[3,40-43, 68], it is possible that the duration and intensity of the exercise training (either IMT or aerobic) may not be adequate to induce measurable changes in cardiac geometry and or to systolic and diastolic physiological performance.

Human Subjects

A. Risk to Subjects

A. Human Subjects Involvement and Characteristics

The study population will consist of 75 male and female participants age 50 and older who have been diagnosed with systolic heart failure (HF). Recruitment will include only Veterans and will focus on the VA Boston Healthcare System for recruitment. All patients must be cleared by their physician to participate in a supervised exercise environment.

As indicated in the Methods section:

Inclusion Criteria

- NYHA class II or III or AHA stage B or C HF with reduced ejection fraction (≤45), or AHA stage C with preserved ejection fraction despite a minimum of 6 weeks of optimal treatment

- Age ≥50 years

- Optimal therapy according to AHA/ACC and HFSA HF guidelines, including treatment with ACEI and beta-blocker therapy (for at least 6 weeks), or have documented reason for variation, including medication intolerance, contraindication, patient preference, or personal physician's judgment.

  ✓Patients using statins will be enrolled; in the pilot study it was evident that most patients eligible for this study were on statins since prevalence of hypercholesterolemia is high and most clinicians are attentive to prescribing statins as part of their standard of care. While this is potentially a confounding issue, we will be certain that statin use is balanced in each arm.

Exclusion Criteria

- Major cardiovascular event or procedure within the prior 6 weeks.
- HF secondary to significant uncorrected primary valvular disease (except mitral regurgitation secondary to left ventricular dysfunction). If valve replacement has been performed, patient may not be enrolled for 12 months after this procedure.
- Dementia
- Severe COPD (FEV1<50%),
- PVD that would limit exercise- End-stage malignancy
- Orthopedic exercise limitation
- Women who are pregnant, breastfeeding, or likely to become pregnant within the next 6 months
- Psychiatric hospitialization within the last 3 months
- Chronic ETOH or drug dependency.
- Exclusion criteria: Patients who have very poor acoustic windows in whom it is deemed that even with the use of contrast adequate image acquisition will not be possible will be excluded after initial assessment

B. Sources of research materials

All information pertaining to this project (e.g., screening forms, questionnaire data, interviews, cardiopulmonary testing results) will be held in the strictest confidence, will be kept in locked files, and will be available only to individuals directly involved with the project. Under no circumstances will individually identifiable data be released to anyone without written consent of the participant. Results will be published as group findings only. Assessment and treatment results will be discussed with the participant only and will only be used for research purposes unless patient give clearance for information to be provided for their own clinical care.

C. Potential Risk - During Assessments: - Controls only functional testing for all other patients will be completed as part of the Exercise Therapy protocol.

- During exercise testing assessments, just as when taking part in any exercise there are inherent risks associated. However, all candidates will undergo a cardiopulmonary exercise stress (CPX) test as part of their enrollment to provide baseline exercise indices, but also to provide a means to screen for safety prior to exercise training. Patients' physicians will refer only patients they expect to be stable. , A physician , will examine all study candidates before CPX and will also supervise the exercise tests to maximize safety. All testing will be completed by ACLS trained staff and during the stress test the physician will work in combination with an exercise physiologist to insure patient safety.

- Maximal exercise testing is associated with a 1 in 10,000 chance of significant untoward outcome (e.g., myocardial infarction, arrhythmia), including the possibility of death. However, all those enrolled will have a physical exam immediately before to best insure they are stable and they will have a physician performing the stress test to be sure they are maximally safe and well cared for if any problems develop. The physicians, cardiologist, nurse practitioner and study exercise testing personnel are all ACLS trained and a code cart is in the immediate vicinity. Testing is only completed when the hospital Urgent Care center is open to provide back-up medical services.
- Other problems that might also develop from a stress test include skin reactions to the electrode leads. Men may also need to have parts of their chest hair shaved in order to attach electrodes; this hair grows back over the next few weeks.
- CPX involves breathing through a small snorkel device. In some cases, people feel the snorkel is uncomfortable, and that the air seems dry. Water will be available in the immediate vicinity
- Patients will answer questionnaires as part of the study assessments, i.e. requiring responses about daily activities, diet, quality of life and sleep which in some cases may be a source of emotional distress. Efforts will be made to keep the environment and support by staff to be reassuring and pleasant.
- Subject fatigue is a possibility during the comprehensive physical assessment battery that is completed as part of the protocol. However, as noted in the Methods, precautions have been integrated with the assessments to minimize risk to the subjects. Rest periods are provided after each active functional assessment, moreover, active functional assessments alternate with ones that are completed at rest (questionnaires and endothelial assessments). Furthermore, before each stage of the functional assessment, heart rate and RPE is reassessed to make sure that the subject has returned to baseline of physiological and subjective parameters.

D. Therapeutic Risk-

- Echocardiography:

All echocardiographic examinations will be performed at the West Roxbury VA campus by well trained sonographers. West Roxbury VA echo lab is a fully accredited lab by ICEAL. All echocardiographers performing the examination are board certified and credentialed by ICEAL. Standard echocardiographic equipment will be used and image acquisition will be performed in accordance with the standards proposed by the American Society of echocardiography. Patient privacy and confidentiality will be maintained during the entire procedure. Efforts will be made to keep the environment and support by staff to be reassuring and pleasant.

Standard echocardiographic examination is non invasive and therefore there are no inherent risks associated with this procedure. However about 10% of the patients may not have adequate acoustic window for image acquisition. In this group of patients intra-cavitary echo contrast will be used for better endocardial border delineation. Contrast will be administered through a peripheral IV.

- Risks associated with this will include the inherent risks of a peripheral IV and risks associated with contrast administration which are as follows. Rare allergic reactions at an approximate rate of 1/10,000,
- Other adverse effects include headache, weakness, fatigue, palpitations, nausea, pruritus and back pain. Potentially life threatening reactions could occur although very rare. (In our laboratory we perform >4000 echo per year and use contrast in at least 10% of our pts. In the last 8 years we have never had a single serious reaction).

Contraindications for administration of contrast include

a) right-to-left, bidirectional, or transient right-to-left cardiac shunts
b) hypersensitivity to perflutren
c) hypersensitivity to blood, blood products, or albumin (applies to Optison only).

2. Adequacy of Protection from Risk

A. Recruitment and Consent Procedures

The VA Boston is a large cardiovascular clinical center, encompassing 3 campuses (Jamaica Plain, West Roxbury, and Brockton) and several community based outpatient clinics (CBOC), with a high volume of heart failure seen throughout these campus. The plan will be to recruit 45 patients in year one, and 30 patients during year two, for a total of 75 participants. Primary recruitment for this study will occur as part of the already funded research project VA Merit F0834-R entitled "Exercise Therapy to Reduce Heart Failure Symptoms; Sorting Mechanisms of Benefit" (Site-PI, Gottlieb; PI, Forman). Additionally control subject will be recruited through heart failure clinic, echocardiogram clinic and flyers post.

Only individuals who provide written informed consent may participate. In accordance with informed consent and HIPAA regulations, written informed consent and HIPAA forms will be obtained from each participant after a thorough explanation of procedures by a project staff person and the opportunity for the participant to ask and receive answers to questions. Participants will be informed of the nature of the investigation, the types of assessments and treatment involved, the potential risks involved in participation and will be asked to sign an informed consent statement prior to participating in the proposed study. In addition, participants will receive an explanation of how their information will be handled including all parties involved, data management, and plans to publish data in group format without identifying information. The Institutional Review Board of VA Boston Healthcare System will approve the protocol, consent, and authorization forms. Participants will also be informed that they are free to withdraw from the study at any time without any consequences.

B. Protection Against Risk

We will carefully screen to identify individuals whose risk for potential adverse outcomes is elevated were they to participate in the proposed research. All participants will have a thorough review of their medical records prior to enrolling in the study by study staff and study physicians. To determine stability prior to beginning exercise all participants will have a physical exam performed by a study cardiologist, physician or nurse, complete an exercise stress test that will be administered by trained personnel and supervised by a cardiologist, physician, or nurse practitioner.

Participants will be instructed to contact study personnel at any time if they are having any problems.

Participants who begin treatment and experience adverse outcomes sufficient to require removal from the study will receive appropriate clinical care. As in any type of treatment or clinical research program, participants' confidentiality must be carefully guarded and respected.

All data with identifying information will be stored in locked files or password-protected computer files. Data being analyzed will be identified by subject codes, and identifying information will be removed. The identity of participants will not be revealed in the presentation or publication of any results from the project. All project staff working on the project will be educated about the importance of strictly respecting participants' rights to confidentiality and will have completed several training courses including proper practice in accordance with HIPAA regulations, protection of human subjects, and computer security. The codes that link the names of participants and their ID numbers will be kept confidential by the PI in a secured cabinet located within his office. These data will only be accessible to the PIs and staff directly working with the study.

All personnel proposed for this project will have the required human subjects and confidentiality training, which includes information about maintaining data integrity and security. Confidentiality will be guarded using established procedures such as storing data in locked cabinets within locked offices or locked data rooms, coding by study identification numbers rather than any personally identifying information to avoid revealing the identity of subjects, and aggregating data across participants. The key linking names and study identification numbers will be kept separately from the data sets with limited access by study personnel. Only study personnel will have access to the data sets on protected servers. In order to maintain the highest standard of data entry quality, all data will be double-entered, with discrepancies highlighted so that they can be reviewed by the project coordinator. Oversight of all aspects of data management will occur with the PIs.

3. Potential Benefits of the Proposed Research to the Subjects and to Others.

The direct benefit to participants who enter this study will be to obtain the opportunity to exercise in a supervised environment.

4. Importance of the Knowledge to be gained

The exercise intervention proposed in this study has the potential to help Veterans manage their HF, improve quality of life. Results from this study will inform the development of clinical interventions for how to better treat patient with HF with in exercise routines. In addition, results will provide information about the feasibility and patient satisfaction associated with this type of treatment. These findings will guide development of treatment with in clinical setting.

5. Data Safety Monitoring Plan

Monitoring of safety and data quality in the proposed study will be the responsibility of all personnel on the project, with primary responsibility and supervision by the PI. Both the VA Boston Institutional Review Board will approve the Statement of Informed Consent for the study and provide institutional oversight of data and safety issues. The study protocol will be approved prior to recruiting or consenting any participants. Moreover, the study will be reviewed on an annual basis by the IRB committee. The CSR&D office will be appraised of any issues raised in these reviews. Each participant will sign the Informed Consent Form described above prior to participating in the study. To ensure participant safety, once participants are enrolled in the study, study staff will immediately report all adverse and serious adverse events to one of the PIs. The PI will, per standardized procedures, report them to the IRB for their review. With regard to monitoring of data quality and protected health information, all required personnel proposed for this project will have the required human subjects and confidentiality training, which includes information about maintaining data integrity and security. Confidentiality will be guarded using established procedures such as storing data in locked cabinets within locked offices or locked data rooms, coding by study identification numbers rather than any personally identifying information to avoid revealing the identity of subjects, and aggregating data across participants. The key linking names and study identification numbers will be kept separately from the data sets with limited access by study personnel. Only study personnel will have access to the data sets on protected servers. In

order to maintain the highest standard of data entry quality, all data will be double-entered, with discrepancies highlighted so that they can be reviewed by the project coordinator. Oversight of all aspects of data management will occur with the PIs.

Data Monitoring Plan. Data will be collected using standardized forms and will only be identified using the participant's ID number (no names or identifying information will be on the forms). The codes that link the names of participants and their ID numbers will be kept confidential by the PI in a secured cabinet located within his office. These data will only be accessible to the PIs and staff directly working with the study. All data will be entered on-line, with 100% review by the project coordinator in those instances where a discrepancy occurs during double entry. Data will be entered in the computer independently by trained data entry staff, and data entry discrepancies will be corrected by the project coordinator, based on source documents. The quality of the data will be monitored on an ongoing basis. Data quality will be monitored by inspection of the completed forms by a research assistant and any problems detected will be discussed with the PIs.

In the proposed study we will use the FDA definition of adverse events (AE) and serious adverse events (SAE). Any SAE, whether or not related to study intervention, will be reported immediately to the IRB and will be followed by an additional letter detailing the nature of the SAE. In the event that a participant either withdraws from the study or the PIs decide to discontinue a participant due to a SAE, the participant will be monitored by the co-PIs until (a) a resolution is reached (e.g., the problem has resolved or stabilized with no further change expected), (b) the SAE is determined to be clearly unrelated to the study intervention, or (c) the SAE results in death. Outcomes of SAEs will be regularly reported to the VABHS IRB. A summary of the SAEs that occurred during the previous year will be included in the annual progress report as well as in the annual IRB renewal. Suicidal ideation and AEs will be formally assessed immediately after treatment and referrals for further care will be made as needed. The study will be conducted at VA Boston Healthcare System. Under the arrangement to conduct the study on site at the VA facilities, the VA agrees to provide emergency services to anyone who participates in this project. We will have specifically outlined in the Informed Consent Forms the availability of emergency services to participants who may seek them during and after normal working hours. In the Informed Consent Form, we will provide specific information about emergency contacts. Participants are instructed to contact Dr. Aragam during working hours. After hours participants will be provided the information on how to contact the cardiology fellow on call. We will also provide a list of crisis hotline numbers and community resources that participants may access as well as making sure the Veterans have access to the Suicide Prevention Hotline for Veterans (1-800-273-TALK).

Inclusion of Women, Minorities, and Children

Women: The investigators will make proactive attempts to insure that women are adequately represented in this study. As CHF is becoming a progressively more common disease in this population as they age. Approximately 2748 women are treated annually at the VABHS, and there are specialized women's services from where we can conduct a more focused recruitment effort. The Women's Health Center has been recognized for outstanding care with the VA Clinical Program of Excellence Award and the Department of Health and Human Services Center of Excellence Award.

Minorities: The investigators will insure that minority populations are adequately represented in this study by utilizing a stratified recruitment approach. Statistics provided by Medical Administration indicate that the population represented in this facility is 7% Black or African American, 1.6% Hispanic, .5% Asian, Pacific Islander, American Indian or Alaska Native, and 92% Caucasian. Moreover, the BWH Heart Failure Program has approximately 30% minorities. In order to obtain a sample that is more representative of minority populations, we will oversample underrepresented groups.

Children: Individuals under age 18 will not be included in the proposed project