Project Narrative

Introduction
Heart failure is a serious condition, which is commonly caused by the inability of the heart to contract properly (ejection fraction at rest is <40%). It is a significant health care issue in the United States, with total cost of care of about 30.7 billion dollars yearly (1). About 5.7 million people in the United States (≥20 years) have heart failure (2), and nearly 900,000 new cases (≥55 years of age) of heart failure are diagnosed each year (2). At 40 years of age, the lifetime risk of developing heart failure in both men and women is one in five (2). Thus, there is a great need in creating successful interventions to mitigate these costs, as it is projected that the prevalence of heart failure will increase to 8.5 million people and ~70 billion dollars yearly in 2030 (1).

One successful way to improve outcome in these patients and reduce long-term health care costs is cardiac rehabilitation, which involves regular aerobic exercise training. Moderate aerobic exercise training (> 3x per week, about 40 to 60 minutes per session, 60 to 75% of peak heart rate) in heart failure patients can improve aerobic capacity (i.e. the highest rate of oxygen consumption during peak exercise, averaged over the final minute of an exercise test) by +2.2 to +2.6 mL/kg/min (3, 4). This degree of improvement in aerobic capacity not only has the potential to significantly reduce health care cost (5) (see Figure 1), it also translates to an 8-9% improvement in survival (6) in all types of patients, including those with heart failure.

Figure 1. The one-year cost by exercise performance given in METS (Metabolic Equivalents). 1 MET = 3.5 mL/kg/min, which is the oxygen consumption at rest. So, five METS during exercise would be 5 x 3.5 mL/kg/min or 17.5 mL/kg/min. Five groups are shown, which include about 62 patients with heart failure. The most deconditioned group has an aerobic capacity of < 5 METS, the most conditioned group ≥11 METS. In unadjusted analysis, costs were incrementally lower by an average of 5.4% per MET (per 3.5 mL/kg/min) increase (p < 0.001). The data shown are the median with 25th and 75th percentiles.
From Weiss et al. (2004)(5)

However, what if there was a way to safely improve aerobic capacity to a higher level, thus further improving survival and reducing health care costs even more than the usual care of moderate intensity exercise? The current guidelines support moderate intensity exercise training in heart failure patients (7) since there is a 15% reduction in cardiovascular mortality or heart failure hospitalization compared to a control group (8). High intensity interval training, in which an individual exercises at ≥ 85% of peak heart rate for 3-4 minutes at a time, followed by 3-4 minutes of active rest at ~40% of peak heart rate (HR), may be a promising strategy. In a meta-analysis of 277 individuals with cardiometabolic disease (one or more of coronary artery disease, heart failure, diabetes, obesity, metabolic syndrome), aerobic capacity increased by +5.4 mL/kg/min (+1.5 METS, or ~20%) (3). This, theoretically, reduces yearly health care costs by ~8.3%, more than twice that of the moderate-intensity exercise groups according to the data from Weiss and colleagues (5). This improvement also confers a ~19% improvement in survival (6), again, more than twice that of moderate intensity exercise.

Some papers have discussed the use of high intensity aerobic exercise in those with chronic heart failure (9-11). These papers state that although promising, more research is needed before high-intensity interval training can be recommended as safe and effective for patients with stable, chronic heart failure. There are only a few studies using high intensity training in heart failure patients, but those studies demonstrate better outcomes compared to moderate intensity exercise (12-14). Functional outcomes such as oxygen uptake (12-14), power output on a cycle ergometer (14), and cardiac output (14) at peak exercise, as well as quality of life (13) are better after several weeks of high intensity exercise training compared to a similar length program of moderate intensity exercise (Table 1). As well, there is evidence that there is reversed left ventricular remodeling after 12
weeks of high intensity aerobic training compared to moderate intensity exercise. For example, after 12 weeks of high intensity interval training, measurements of left ventricular end-diastolic diameters, and end-diastolic and end-systolic volumes declined by 12-25%, ejection fraction increased from 28% to 38%, while cardiac output increased by 12% at rest (13). The group that did moderate-intensity exercise did not show these improvements. Moreover, plasma N-terminal pro b-type natriuretic peptide (NT-proBNP), a marker of severity of heart failure, declined by 40% to 750 pg/mL after high intensity interval training (13) (Table 1), but not after moderate intensity exercise training.

Is high intensity interval training safe in heart failure patients? Yes, it seems so (Table 1). In one study, high intensity interval exercise decreased the amount of arrhythmias in those with heart failure. Using a Holter ECG recording system on 18 chronic heart failure patients (ejection fraction < 40%), premature ventricular contractions (PVCs) decreased to 531 PVCs in the following 24 hours after a single bout of high intensity interval training, compared to 1007 PVCs in the following 24 hours after a single bout of moderate intensity exercise, compared to 1671 PVCs in the following 24 hours after no exercise (10). There is also a reduction in ventricular arrhythmias in diabetic rats that performed high intensity interval training after a myocardial infarction (15). In a study that included ~339 heart failure patients, the cardiovascular event rate for high intensity exercise (85-95% of peak HR for 4-minutes at a time) was found to be low, at one event per 23,182 hours (16). Thus, this early data suggests that high-intensity interval training can be performed safely and effectively in stable heart failure patients. However, while there is some evidence that high intensity aerobic exercise is beneficial to heart failure patients, there is limited data on functional outcomes, which is a shortcoming of Table 1. Only 36 heart failure patients are involved in studies that compared high intensity interval training with moderate continuous exercise in which aerobic capacity was measured (12-14), and only ~25 subjects had cardiac output measured at rest (13, 14), and only ~15 patients had cardiac output assessed at peak exercise (13). Thus, this proposal is unique in that we measure functional outcomes at rest and peak exercise in these patients using highly sophisticated measurement devices. Furthermore, there is only one study to examine left ventricular modeling of the heart from high intensity training (13), and this proposal will address that gap, too.

<table>
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<tr>
<th>Table 1: Benefits of high intensity interval training compared to moderate intensity exercise training in heart failure patients</th>
<th>Studies</th>
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<tbody>
<tr>
<td><strong>Functional outcomes at peak exercise</strong></td>
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<tr>
<td>~3-5 mL/kg/min higher peak oxygen uptake</td>
<td>(12-14)</td>
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<tr>
<td>~1.5 mL/beat higher peak oxygen pulse</td>
<td>(12)</td>
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<tr>
<td>~22 W higher peak power output</td>
<td>(14)</td>
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<tr>
<td>~3 L/min higher peak cardiac output</td>
<td>(14)</td>
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<tr>
<td><strong>Functional outcomes at rest</strong></td>
<td></td>
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<tr>
<td>~0.5 L/min higher cardiac output at rest</td>
<td>(13)</td>
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<tr>
<td>~9% Higher ejection fraction at rest</td>
<td>(13)</td>
</tr>
<tr>
<td>12-15% lower left ventricular end diastolic and end systolic diameters at rest</td>
<td>(13)</td>
</tr>
<tr>
<td>18-25% lower end diastolic and end systolic volumes at rest</td>
<td>(13)</td>
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<tr>
<td>40% lower plasma brain (or B-type) natriuretic peptide (proBNP)</td>
<td>(13)</td>
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<tr>
<td><strong>Subjective outcomes</strong></td>
<td>~12% better quality of life</td>
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<tr>
<td><strong>Safety outcomes</strong></td>
<td></td>
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<tr>
<td>~50% lower arrhythmia rates 24 hrs post exercise</td>
<td>(10)</td>
</tr>
<tr>
<td>Low cardiovascular event rate (one event per 23,182 of high intensity exercise)</td>
<td>(16)</td>
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As such, the main goal of this study is to provide additional data on the safety and efficacy of high intensity interval training in stable heart failure patients and to demonstrate better physiological and clinical outcomes with fewer long-term health care costs compared to the standard of care. This preliminary data will be used for a much more comprehensive grant application to the National Institutes of Health. The main specific aims are as follows:
Specific Aims

1. To determine whether cardiac output, ejection fraction, global longitudinal strain (an estimate of left ventricular function (17)), and pulmonary diffusing capacity (how well oxygen travels from the alveoli of the lungs to the blood stream) measured at rest, is increased after 8 weeks of high intensity interval training in stable heart failure patients.

2. To determine whether oxygen uptake and cardiac output at peak exercise is increased after 8 weeks of high intensity interval training in stable heart failure patients.

3. To determine heart rate variability (HRV) and number of arrhythmic events over a 24-hour period after 8 weeks of high intensity interval training in stable heart failure patients.

Study Methodology

Participants: Twenty stable outpatients (10 men and 10 women), with chronic heart failure will be recruited from the Grady Cardiac Clinic to participate in an 8 week (32 sessions), supervised, exercise-training study. These subjects will exercise train under the watchful eye of healthcare professionals at the Cardiac Rehabilitation Clinic at Emory St. Joseph’s Hospital. The inclusion criteria are as follows: (1) stable, chronic heart failure with a left ventricular ejection fraction of 40% or less, (2) New York Heart Association (NYHA) class I to III symptoms with treatment that includes beta blocker and angiotensin-converting enzyme inhibitor therapy for at least six weeks, (3) no recent major cardiovascular hospitalizations or procedures within the previous three months, (4) Age 40-60 years, (5) aerobic capacity $\geq 12$ mL/kg/min, (6). Exclusion criteria are as follows: inability to exercise (orthopedic or neurological problems), history of seizure disorders, history of atrial fibrillation, presence of pacemaker, uncontrolled diabetes mellitus, diabetic insulin pump, uncontrolled hypertension, renal insufficiency (creatinine: $> 2.5$ mg/dl), severe left ventricular hypertrophy ($> 1.8$ cm wall thickness) or dynamic left ventricular outflow tract obstruction, greater than mild degree of valve stenosis or presence of an artificial heart valve, drug addiction, and signs of unreliableness. These patients will be divided into one of two groups based on their sex and aerobic capacity. The patients will be randomly assigned in blocks of two so that number of males and females per group would be similar and the average aerobic capacity per group are similar. Based on the first baseline aerobic capacity results, all the women and men will be ranked separately from highest to lowest based on their aerobic capacity. One of the two highest ranked women will then randomly be assigned to one of the study groups and the other woman to the other study group. This would then continue for the next two fastest women, and so on. The men will be assigned groups in the same way.

Procedures: Subjects will undergo two baseline cardiopulmonary exercise testing sessions, one for familiarization, and the other for measurement. This will allow for determination for the repeatability of the procedures in these patients. Then the patients will undergo 8 weeks of exercise training at a frequency of 3-4 days per week (Table 2). Successful compliance will be determined as participating in 75% of the available sessions (24 out of 32 sessions). The sessions will be monitored by an American College of Sports Medicine Registered Clinical Exercise Physiologist (ACSM-RCEP®) or by one of the staff members at Emory St. Joseph’s Hospital. Heart rates will be directly measured via blue booth (Polar FT1 training computer, Polar T31 coded transmitter, Lake Success, NY). Blood A1C (average blood sugar level in the past 2-3 months), and a comprehensive blood panel will be measured at baseline and at follow-up in each patient.

The Borg scale for rating of perceived exertion (RPE) (18) and the heart rate reserve (HRR) method will be used to gauge exercise intensity. For example, 50% of HRR = 0.5·(peak HR − resting HR) + resting heart rate. Resting HR and peak HR will be measured directly since estimations based on the “200 – age“ or the “208 – 0.7·(age)” formula are inaccurate (19, 20). Additionally, beta blocker therapy will likely blunt the chronotropic response, so the HRR method is preferred. The RPE scores will also supplement the HRR method for intensity. During each training session, the number of adverse events will be recorded (i.e. cardiac arrest, myocardial infarction during exercise, or within the first hour afterward). As well, body weight and blood glucose values will be measured prior to each exercise session. A value below 100 mg/dL trigger these participants to eat a small carbohydrate-containing snack, such as fruit or crackers, prior to exercise. Following the eight-week training program, patients will then undergo follow-up cardiopulmonary exercise testing.
24-hour Holter electrocardiographic (ECG) monitoring: Patients will be given a Holter monitor for assessment of HRV and arrhythmias over a 24 hour period. The patients will be given a monitor at baseline and at the end of their final exercise training session as described previously by Guiraud et al. (10).

Table 2: Eight week (32 sessions) isocaloric exercise training program.

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<th>High intensity interval training program (AIT)</th>
<th>Moderate-intensity training program (MIT)</th>
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<tr>
<td>Weeks 1-2</td>
<td>Each session: Warm-up at 10 minutes at 40% HRR. Then, 3 x 4 minutes at 80% HRR. The rest between each 4 minute interval is separated by 3 minutes of active recovery at recovery at 30-40% of HRR. Then a 3 minute cool down at 30-40% of HRR = 31 minutes total, RPE = 16</td>
<td>Each session: Continuous exercise at 50% HRR for 40 minutes. RPE = 12</td>
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<tr>
<td>Week 3-4</td>
<td>Each session: Warm-up at 10 minutes at 40% HRR. Then, 4 x 4 minutes at 85% HRR. The rest between each 4 minute interval is separated by 3 minutes of active recovery at recovery at 30-40% of HRR. Then a 3 minute cool down at 30-40% of HRR = 38 minutes total, RPE = 16</td>
<td>Each session: Continuous exercise at 55% HRR for 47 minutes. RPE = 13</td>
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<tr>
<td>Weeks 5-8</td>
<td>Each session: Warm-up at 10 minutes at 40% HRR 4 x 4 minutes at 90% HRR. The rest between each 4 minute interval is separated by 3 minutes of active recovery at recovery at 30-40% of HRR. Then a 3 minute cool down at 30-40% of HRR = 38 minutes total, RPE = 17</td>
<td>Each session: Continuous exercise at 60% HRR for 47 minutes. RPE = 14</td>
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<tr>
<td>Total</td>
<td>856 minutes of exercise (14.3 hrs)</td>
<td>1072 minutes of exercise (17.9 hrs)</td>
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RPE = rating of perceived exertion, Borg 6 to 20 scale (18); RPE of < 10 is very light, RPE of 17-19 is very hard

Baseline and Post-testing: In the Petit Science Center (Room 457) at Georgia State University, patients will undergo baseline pulmonary function testing including spirometry, lung volumes and diffusing capacity using the pulmonary function system from MEDISOFT (HypAir, Dinant, Belgium). The American Thoracic Society / European Respiratory Society guidelines for lung function testing will be followed (21-25). Then, patients will undergo a cardiopulmonary exercise test to volitional fatigue on an electronically braked cycle ergometer. First, oxygen uptake, carbon dioxide production, expired ventilation, and heart rate will be measured at rest with a breath-by-breath metabolic measurement system (CosMed Quark CPET, Rome, Italy). Then, cardiac output and diffusing capacity will be assessed via rebreathe technique sampled from a respiratory mass spectrometer (Perkin Elmer MGA 1100, Pomona, CA) and a nitric oxide chemiluminescent analyzer (Sievers NOA 280i, GE Analytical Instruments, Boulder, CO) using custom analysis software based on the formulas from Triebwasser and colleagues (26). The rebreathing technique is described by our group elsewhere [see section 2.3, page 23, from Zavorsky and colleagues (27)]. Then, the exercise test will begin at 20 W (80 rpm) and will increase every 3 minutes in a step fashion until volitional fatigue. Fatigue is estimated to occur at ~80 W in these patients (14), or ~12 minutes. Patients will be asked again to perform the rebreathing maneuver again for an assessment of cardiac output and diffusing capacity at peak exercise. Transthoracic echocardiography will be performed at baseline and after eight weeks of training to evaluate left ventricular size and function. 24-hour ambulatory ECG monitoring (Holter) will also be performed at baseline and at study end to evaluate measures of arrhythmia. Quality of life will be measured via the MacNew heart disease questionnaire (28) at baseline and again eight weeks post-training.

Research design: The research design will be a pre-post test design with control group, where the control group is the standard of care group (moderate-intensity exercise group). This is a quasi-experimental design in which a convenient sample of patients with stable heart failure patients is used. Patients will be placed into one of two groups randomly by blocks of two, controlling for sex and aerobic capacity.

Sample size calculation: The sample size estimated is based on functional outcomes. The main independent variable in this study is the two different types of exercise training. The main dependent variables measured will be cardiac output, ejection fraction, and pulmonary diffusing capacity at rest, as well as cardiac output and
oxygen uptake at peak exercise. Based on a 3 (SD 2.5) L/min improvement of peak cardiac output in the high intensity interval training group and no improvement in the moderate intensity group (14), about 8 patients per group in total will be needed (Effect size = 1.2, statistical power = 80%, alpha error probability, t-test family = difference between two dependent means, G*Power 3.1.9.2, Universität Kiel, Germany). Accounting for a ~20% attrition rate (2 subjects) per group, a total of 20 subjects will be recruited (10 per group).

**Statistical Analyses:** A 2 x 2 repeated measures analysis of variance (ANOVA) will be used to examine the first two specific aims (2 groups; 2 time-points: baseline, post-training). A repeated measures design also provides us the opportunity to control for individual differences among participants. To compare groups, baseline subject characteristics (including anthropometric data, environmental conditions) independent t-tests will be performed. If any of the variables are not normally distributed (as verified by a Shapiro-Wilk test), then a Mann-Whitney t-test will be used to compared groups. A Fisher’s exact test will be used also used to compare groups for the number of arrhythmias reported 24-hours after the final exercise training session, as well as examining the number of various cardiovascular events reported during the training. Statistical significance will be set at 0.05. Analyses will be performed using IBM SPSS Statistics (Version 21.0, IBM Corporation, Armonk, NY).

**Protection of Human Subjects:** Prior to group assignments, these patients will be notified of the benefits and risks associated with the study through informed consent. The protocol for the study will be discussed in detail to ensure everyone will be aware of the expectations involved, and they will be informed of their rights as participants in the study. After providing this information, the patients will provide informed consent. The Institutional Review Board (IRB) of both Emory University and Georgia State University will review this study as well as the IRB committee at Emory St. Joseph’s Hospital and the research oversight committee at Grady Memorial Hospital.

**Anticipated Results**
After 8 weeks of high intensity interval training, cardiac output will increase by a mean of 0.5 L/min at rest, ejection fraction will increase by a mean of 10% at rest, and pulmonary diffusing capacity will increase by 4 mL/min/mmHg more at rest compared to the group that does moderate intensity exercise training. As well, oxygen uptake and cardiac output at peak exercise will increase by a mean of 3.5 mL/kg/min (1 MET) and 3 L/min, respectively, compared to the group that does moderate intensity exercise training. Finally, after 8 weeks of high intensity training, the HRV indices will increase, and the number of arrhythmias (i.e. PVCs) will be 50% less compared to the group that does moderate intensity exercise training.

**Significance of the Project**
There is little data on the functional benefits effects of this type of training in heart failure. This study will help reinforce the safety and efficacy of this type of training in these patients. This study will add to the literature in demonstrating that high intensity interval training is a better method of cardiac rehabilitation compared the current recommendations. The project will provide evidence to improve cardiac rehabilitation for heart failure patients around the world. As such, it is an extremely important and timely study.

**Potential for successful study completion:** The research team has the ability to be successful in this project. Dr. Zavorsky is a clinical exercise physiologist who has published over 50 peer-reviewed papers, most of which involved cardiopulmonary exercise testing. He has performed exercise studies in cancer (29, 30) and morbidly obese patients (31). He has a highly sophisticated lab that can measure functional outcomes properly (27). He will perform all baseline and follow-up cardiopulmonary testing. Dr. Niels Engberding, MD, FACC, FESC, a co-investigator of this study, is a cardiologist with clinical expertise in cardiac stress testing and echocardiographic assessment of heart failure patients. He will perform the physical evaluation of each subject and he will assess the data from the echocardiography testing and Holter monitoring and help with recruitment. Dr. Basil Margolis, MD, FACC, is the Medical Director of the Center of Preventative Cardiology at Emory St. Joseph’s Hospital and is supportive of this project. Jocelyn Disher, MSN, RN, unit director of Cardiac Rehabilitation, and Kathy Bishop, DPT, program manager of Emory St. Joseph’s Cardiac Rehabilitation program, has organized the scheduling in their facility so that the study subjects are able to use their Center.
References

7. McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Bohm M, Dickstein K, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur Heart J. 2012;33(14):1787-847.


