Study Title: Study of the Effects of Caloric Restriction and Exercise Training II (SECRET II)

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Amendment 51

A limited dataset of demographics, clinical variables, and outcomes measures will be sent via encrypted files to Dr. Ambarish Pandey, MD at UT Southwestern. Additionally, deidentified extracted DNA samples will be sent for CHiP analyses. A Data Use Agreement and Material Transfer Agreement will be completed with the Office of Sponsored Programs.

Background, Rationale and Context

Heart failure with preserved ejection fraction (HFpEF) is a relatively recently recognized disorder and the fastest growing form of HF.(170; 180) HFpEF is nearly exclusively found in older persons, particularly women, in whom 90% of new HF cases are HFpEF.(85) HFpEF is associated with markedly increased morbidity, mortality, and health care expenditures.(12; 86; 136; 193) Despite its importance, the prognosis of HFpEF is worsening, its pathophysiology is poorly understood, and other than diuretics no medications have proven effective.(170; 197; 229)

Exercise intolerance, with severe exertional dyspnea and fatigue during normal activities, is the primary manifestation of chronic HFpEF and a major cause of reduced quality of life (QOL).(28; 125) Our work has focused on understanding the pathophysiology of HFpEF and testing strategies to improve exercise intolerance.(8; 31; 96-98; 110; 118; 124; 125; 127; 128; 178; 190) Peak oxygen consumption during exercise (peak VO_2) is a widely accepted primary outcome in HF trials,(9; 89) including older HFpEF patients,(89; 190) because it provides an objective, standardized, valid, reproducible measure of exercise intolerance,(11; 21; 190) is an independent predictor of QOL, hospitalizations and mortality, and is sensitive to interventions that improve the underlying abnormalities.(11; 63; 89; 127; 128)

Peak VO_2 is determined by the combined contributions of cardiac, arterial, and skeletal muscle function.(11) As recently cited by others, our work has helped change the conventional paradigm of chronic HFpEF,(27; 115; 146; 197) by demonstrating that in addition to cardiovascular dysfunction, older HFpEF patients have multiple skeletal muscle abnormalities, including adipose infiltration, reduced muscle mass, capillary density, type 1 oxidative fibers, citrate synthase activity, and mitochondrial content and these strongly contribute to their severely reduced peak VO_2.(94; 98; 100; 120; 164) As first reported in a randomized trial by our group,(128) aerobic exercise training (AT) remains the only intervention that improves peak VO_2 in HFpEF.(116) Our work and others' indicate that improvements in skeletal muscle function account for nearly all the improvement in peak VO_2 with AT.(78; 99; 123; 127) This recent understanding of the key role of skeletal muscle abnormalities mirrors that of two other conditions related to HFpEF: aging and HF with reduced EF (HFrEF). Loss of muscle is a major factor in the age-associated decline in peak VO_2.(64) Aging is also associated with reduced capillary density(48), accumulation of intermuscular adipose,(53; 187) and alterations in mitochondrial mass and function,(47; 186) all associated with reduced peak VO_2, strength, and endurance(17; 133; 164; 187; 214; 215) Furthermore, in HFrEF, decreased skeletal muscle mass, oxidative capacity, and mitochondrial content and function all contribute strongly to reduced peak VO_2 and its improvement after AT, and are not due merely to deconditioning.(43; 46; 56; 57; 73; 84; 93; 131; 142; 149; 150; 199; 212)

Obesity is one of the strongest risk factors for development of HFpEF.(91; 121; 166; 182; 194) About 85% of older HFpEF patients are overweight/obese, twice the general aging population, making obesity a major yet under-recognized contributor to the HFpEF phenotype.(91; 182; 196) Increased adiposity markedly impairs physical function, skeletal muscle composition, and mitochondrial function,(23) as well as cardiovascular function. In obese older adults, weight loss improves body composition and physical, cardiac, vascular, skeletal muscle, and mitochondrial function.(19; 44; 184; 213) However, weight reduction therapy is controversial in HF patients because observational studies uniformly report that overweight/obese HF patients, including specifically HFpEF, appear to have better survival.(10; 45; 69; 91) Recently surgical weight reduction was reported to prevent the onset of HF, and to improve peak exercise intolerance in HFrEF.(151; 200) To date, there have been no published studies of dietary weight loss in any type of HF. Our recently completed study challenges conventional HF

paradigms as the first dietary weight loss intervention for HFpEF. It found that caloric restriction (CR) significantly improves peak VO_2, other measures of exercise capacity and QOL. The improvements were related to reduced total and intermuscular fat and increased mitochondrial content. CR and AT were additive and the combination of CR+AT produced robust improvements in peak VO_2 and QOL. This suggests CR+AT as a novel treatment for the 1.8 million patients with the overweight/obese HFpEF phenotype.

However, 35% of the weight lost during CR in our HFpEF patients was muscle mass and this was not prevented by the combination with AT. This is concerning because muscle mass is a major determinant of peak VO_2 such that the loss of muscle mass may have limited even further increases in peak VO_2 with CR+AT. Although CR+AT strongly increased peak VO_2, about 75% of the deficit in peak VO_2 in HFpEF vs. controls remained, indicating ample opportunity for further improvement.(15) Thus, a strategy that helps preserve muscle mass in the setting of CR+AT may further improve peak VO_2 and its associated functional and QOL benefits for HFpEF. Preserving muscle mass may also: 1) facilitate weight loss and its long-term maintenance since muscle mass is the strongest determinant of metabolic rate;(179; 205; 217; 223) 2) address concerns about exacerbating aging and HF-related muscle loss which is strongly associated with increased disability, hospitalizations, and death;(7; 15; 62; 93; 219) and 3) avoid worsened body composition(18) and reduced physical function that can occur with weight regain after CR when lost muscle mass is replaced disproportionately with fat mass.(14; 15; 18) These factors provide the rationale for retaining skeletal muscle during CR+AT.

Multiple lines of evidence and our preliminary data indicate that resistance training (RT) could be an ideal addition to CR+AT for HFpEF.(184) (1) RT reliably increases muscle mass, quality, strength, and function, significantly more than AT,(37) and specifically during CR.(36; 50; 74; 76; 77; 101; 144; 184; 225) We found that in older non-HF patients undergoing CR, RT reduced loss of lean mass by 47%, and enhanced body composition and physical function(198) - nearly identical to Frimmel et al who found that RT reduced loss of muscle mass by 48%.(74) (2) In HFrEF, RT improves exercise capacity independent of cardiac function and to a similar degree as AT.(177) In older men, RT significantly increased peak VO_2 (+1.9 ml/kg lean/min) and was associated with increased type 1 fiber area, thigh muscle area, capillary density, and citrate synthase (all of which we have found deficient in HFpEF).(76; 77) (3) RT and AT can have additive effects on peak VO_2(20; 49; 144) In HFrEF, the addition of RT to AT doubled the training-related increase in endurance.(20) (4) RT also improves peak VO_2 by mechanisms independent of muscle mass, including muscle mitochondrial function, blood flow, inflammation, and neuromuscular function.(50; 76; 77; 103; 201; 207; 226) Muscle mitochondrial function is a fundamental driver of peak VO_2 and is reduced in older persons and in HFrEF,(50; 76; 77; 104; 201; 207; 226) and is improved by RT in HFrEF.(226) In diabetics, addition of RT to AT improves muscle mitochondrial content, function and oxidative capacity, resulting in increased peak VO_2.(201) Our preliminary data (Sections 3.D.4.) suggest that: a) muscle mitochondrial content is reduced in HFpEF, and b) is related to the increase in peak VO_2 following CR+AT; c) mitochondrial respiratory function is reduced in obese older adults, and d) improves with RT. (5) RT and AT have complementary effects on muscle and cardiovascular function.(52; 92; 95; 101; 103; 144; 157) (6) Regimens adding RT to AT improve compliance.(50; 225) These data provide a strong rationale for the addition of RT to AT during CR.

However, RT has never been tested with CR in any type of HF. Furthermore, there are few data regarding RT in HFpEF; a pilot study used a small dose of RT in combination with AT,(58) and another small study included just 3 HFpEF patients.(177) Although initial concerns have been largely allayed regarding the potential effect of RT on left ventricular (LV) function in HFrEF,(135) there remains equipoise in HFpEF. RT can significantly increase arterial stiffness

and LV hypertrophy(153; 225) a potential concern in HFpEF patients who often already have increased arterial stiffness and LV hypertrophy.(106; 124; 137; 230) Therefore, it is important to rigorously test the efficacy and safety of adding RT to CR+AT, as we propose here using state-of-the-art methods.

Objectives

The **primary** aim is to conduct a randomized, controlled, single-blinded 20-week intervention trial of RT added to CR+AT in 84 overweight / obese (BMI $\geq$ 28 kg/m^2), older (age$\geq$60 years) HFpEF patients to test the following primary hypothesis:

- **The addition of resistance training to CR+AT will improve peak VO_2.**

The **secondary** aims of the study are to test the following secondary hypotheses:

- **Resistance training added to CR+AT will improve retention of skeletal muscle mass.**
- **Resistance training added to CR+AT will improve skeletal muscle mitochondrial function.**
- **The improvement in peak VO_2 with RT will be related to improved skeletal muscle mass and mitochondrial function, and accompanied by improved QOL.**

Peak VO_2 (ml/min) will be assessed by expired gas analysis. Skeletal muscle mass will be measured as thigh muscle area by MRI and total lean mass by DXA.(94; 100) Mitochondrial function and indices of cell death will be assessed by respirometry, protein expression analyses, and enzyme activity assays.(23; 24; 209) QOL will be assessed by the KCCQ instrument. Muscle strength and quality, and cardiac and vascular function will also be assessed.

Methods and Measures

Design

This is a randomized, controlled, single-blind clinical trial. After baseline assessments, 84 patients with HFpEF aged $\geq$ 60 years will be randomly assigned to 1 of 2 groups: CR+AT or CR+AT+RT. Outcomes will be assessed in blinded fashion at baseline and after the 20week intervention. The primary outcome is peak VO_2 (in ml/min) by expired gas analysis during treadmill exercise to exhaustion. The secondary outcome of skeletal muscle mass will be measured by MRI and DXA. The secondary outcome of mitochondrial function will be assessed by respirometry, protein expression analyses, and enzyme activity assays on *vastus lateralis* muscle biopsy samples with RCR as a pre-planned, key outcome. Other measures will include: health-related QOL by the KCCQ instrument, SF-36,EuroQOL,and CES-D. SPPB; lower extremity strength and power by isokinetic dynamometer; muscle quality; 6-min walk distance; thigh composition and LV and arterial function by MRI; and LV diastolic function by echo-Doppler.

Setting

All study tests and procedures will be performed at Wake Forest School of Medicine and Wake Forest University Clinical Research Center. Testing labs include the Cardiac Ultrasound and Stress Testing lab, Clinical Research Unit, Geriatric Research Center, and the Center for Magnetic Resonance Imaging.

Subjects Selection Criteria

Eligible patients will have chronic, stable, well-compensated HFpEF with no changes in cardiac medications or symptoms and no hospitalizations or unscheduled visits for at least 6 weeks prior to enrollment; these criteria minimize status changes and study interruptions.(168) To ensure safety for CR, patients will have a BMI $\geq$ 28 kg/m^2; this cutoff will still include ~75% of older HFpEF patients. HFpEF will be defined using the 2013 ACC/AHA Guidelines and as previously described.(4; 96; 98; 100; 117-119; 124; 125; 127; 128; 181; 210) The 4 key criteria include: clinical signs and symptoms of HF, a normal LV ejection fraction ($\geq$50%) by echocardiogram, LV diastolic dysfunction ($\geq$ grade I)(59; 160) and no evidence of significant ischemic, valvular, pulmonary or other medical disorder to account for their symptoms. As previously reported,(118; 125; 127; 128) clinical signs and symptoms of HF will be defined as either NHANES HF score of $\geq$3 (188) or by the Rich criteria.(185) These criteria produce HFpEF patient characteristics similar to population-based studies(122; 211) and with severely reduced peak VO_2. Patients with contraindications to the assessments (exercise tests, MRI, muscle biopsy) or interventions will be excluded. Final eligibility decisions will be made by a board-certified cardiologist with experience in HFpEF following the conclusion of all baseline assessments.

Inclusion Criteria

1. Clinical signs and symptoms of HF: HF Clinical score ≥3 or Rich Criteria

Heart Failure Clinical Score (≥3 required)

Clinical Variables	Score
Dyspnea/difficulty breathing	
Trouble with breathing (shortness of breath)	1
Hurrying on the level or up slight hill	1
At ordinary pace on the level?	2
Do you stop for breath when walking at own pace?	2
Do you stop for breath after 100 yards on the level?	2
Physical examination	
Heart rate (beats/min)	
91 to 110	1
111+	2
Rales/crackles	
Either lower lung field	1
Either lower and either upper lung field	2
Jugulovenous distention	
Alone	1
Plus edema	2
Plus hepatomegaly	2
Chest x-ray film	
Cephalization of pulmonary vessels	1
Interstitial edema	2
Alveolar fluid plus pleural fluid	3
Interstitial edema plus pleural fluid	3

Or

Rich Criteria

- history of pulmonary edema, or
- occurrence of 2 or more of the following with subsequent improvement with medical therapy and with no other identifiable cause: dyspnea on exertion,

paroxysmal nocturnal dyspnea, orthopnea, systemic edema, exertional fatigue.

2. Preserved Ejection Fraction ≥50%
3. LV diastolic dysfunction (≥ grade 1)
4. Age ≥60
5. BMI ≥28

Exclusion Criteria

- Medical
    A. Valvular heart disease as the primary etiology of HF
    B. Significant change in cardiac medication or HF symptoms <6 weeks
    C. Hospitalization or urgent care visit <6 weeks
    D. Uncontrolled hypertension
    E. Uncontrolled diabetes
    F. Evidence of significant COPD defined as either:
        a. On continuous home oxygen therapy for COPD
        b. Hospitalization for COPD in last 6 months
    G. Recent or debilitating stroke
    H. Cancer or other noncardiovascular conditions with life expectancy less than 2 years
    I. Significant anemia (<10 gms Hgb) (eligibility will be determined by CBC)
    J. Significant renal insufficiency (eGFR < 30 ml/min/1.73 m^2) (eligibility will be determined by comprehensive metabolic panel)
    K. Pregnancy-women of child bearing potential are excluded from participation in this study.
- Psychiatric disease- uncontrolled major psychoses, depressions, dementia, or personality disorder
- Other
    A. Plans to leave area within 1 year
    B. Refuses informed consent
- Screening Echocardiogram
    A. Left ventricular ejection fraction < 50%
    B. Significant valvular heart disease
- Exercise Test
    A. Evidence of significant ischemia
    B. Electrocardiogram: 1mm flat ST depression
    C. Stopped exercising due to chest or leg claudication or any reason other than exhaustion/fatigue/dyspnea
    D. Exercise SBP > 240 mmHg, DBP > 110 mmHg
    E. Unstable hemodynamics or rhythm
    F. Unwilling or unable to complete adequate exercise test
- Magnetic resonance imaging
    A. Indwelling metal-containing prosthesis (orthopedic, valvular, other)
    B. Pacemaker or defibrillator
    C. History of welding occupation (ocular metal debris)
    D. Uncontrollable claustrophobia
    E. Any other contra-indication to MRI
- Thigh muscle biopsy
    A. History of bleeding disorder
    B. Current anticoagulation

C. Contraindication to stopping aspirin for 1 week
D. Allergy to topical anesthetic

Sample Size

Confidence in our estimates is enhanced because they are based on data from our recently completed factorial trial of CR and AT using the same patient population and primary outcome. The chosen sample size has adequate power for the primary and secondary aims and QOL. The effect of CR+AT on peak VO_2 was 110.8 ml/min (7.6% relative effect) with a square root of the mean square error for the ANCOVA model being 107.5. To have 90% power to detect a relative effect due to RT of 5.6% (absolute difference of 82.0 ml/min) in peak VO_2 at the 0.05 two-sided level of significance, the study requires 38 evaluable participants per group. In our recent trial, the retention rate was excellent (93%), similar to our previously published trials in HFpEF. To allow for up to 11% loss to follow-up, a total of 42 subjects per group (84 total) will be randomized. In our recently completed study, we observed a 7.4 cm^2 decrease in thigh muscle area measured by MRI in the CR+AT vs. control group. The square root of the mean square error was 5.98 using analysis of covariance. With 76 evaluable subjects we will have 80% power to detect if the decrease in muscle mass is reduced by 53% (e.g. a difference of 3.9 cm^2). In our study of older, non-HF participants, RT had an effect of this magnitude on muscle retention during CR.(198). We will confirm muscle retention with DXA measurement of total lean mass. In our recently completed study; we observed a 2.2 kg decrease (3.2% relative effect) (square root mean squared error of 28.47) providing 80% power to detect a 2.8% relative effect of RT. This sample size also allows adequate power for the secondary aim, mitochondrial function. In our pilot study, RT increased respiratory control ratio (RCR) from 2.78 to 7.23 (160% increase; mean square error of 6.372). The sample size provides 80% power to detect a 60% increase in RCR. It also provides 80% power to detect a 10% relative difference in the KCCQ QOL score. The sample size also provides adequate power to detect increases in confirmatory measures of exercise capacity. In our recent study, we observed a 35.4%, 13.8%, and 13.9% increase in the AT+CR vs. control group in exercise time, VO_2 reserve, and six-minute walk distance respectively. The sample size provides 90% power to detect a 10%, 8%, and 6% increase in exercise time, VO_2 reserve, and six-minute walk, respectively. We will also have 80% power to detect partial correlations as low as 0.30 at the 0.05 two-sided level of significance to examine independent relationships with peak VO_2.

Interventions

Exercise training overview. The exercise training regimens are based on our successful experience with aerobic training (AT) in 3 randomized trials in HFpEF patients,(127; 128; 156) and resistance training (RT) in 6 trials in older persons with disability due to conditions other than HF(60; 147; 148; 198) These were effective for improving peak VO_2, lean body mass, and QOL(22) and were safe. The exercises are based on ACSM and AHA guidelines for older persons and for HFrEF.(2; 65; 72; 225; 225) The AT and RT interventions are individualized and progressive in nature, beginning at a low level and increasing based on specific milestones (**Table 1**) to safely deliver an optimal stimulus. Both groups (AT-only and AT+RT) will meet 3 times per week for 20 weeks. The total *stimulus* phase of the sessions for both groups will be 50 minutes (30 min for AT and 20 min for RT). To keep the duration similar for both groups, 20 min of light chair-based range-of-motion, stretching, and flexibility maneuvers will be included at the end of the AT-only group sessions. This attention /physical activity control will provide no resistance or aerobic activity. Warm-up and cool-down phases will be 5 min each with stretching, flexibility, and light walking for a total session time of 60 min for both groups.

Table 1	AT Regimen	RT Regimen

Intensity	Initial: 40-50% HRR Goal: 70-80% HRR	Initial: 20-30% 1-RM Goal: 70-80% 1-RM
Amount	Initial: ~15 minutes Goal: 30 minutes	Wk 1-3: 1 set of 8-12 reps Wk 4-20: Addition of 2nd set to volitional fatigue
Type	Walking, treadmill, cycling	6 weight machines: leg curl, leg extension, leg press, calf raise, chest press, compound row

Sessions will be conducted at the Wake Forest Clinical Research Center by Masters-level, Certified Clinical Exercise physiologists with medical supervision to ensure safety and a uniform, robust stimulus. This facility has been used for numerous clinical trials and has appropriate emergency equipment and response team, staff trained in BLS/ACLS. To eliminate potential for cross-group contamination, the 2 groups will meet at different times.

Aerobic exercise training. The AT prescription for each participant will be based on initial evaluations and stress testing results: heart rate reserve (HRR), peak VO_2, RPE. AT sessions will be similar for each group (AT only, and AT+RT) and include a walking circuit, and/or stationary cycling. Initial intensity will start at 40-50% of HRR, calculated by a standard formula(34) and increase gradually for the first 6-8 weeks until the participant can maintain ~60-70% heart rate reserve for at least 20 minutes. Exercise training intensity will be re-evaluated at least every 3 weeks by assessment of heart rate response during submaximal exercise. Depending on subject tolerance, the stimulus duration will progress to 30 minutes, performed continuously or as intermittent bouts. When a subject can complete 30 minutes of continuous exercise, the AT intensity will be increased incrementally to 70-80%. Periodic HR, rhythm, and blood pressure measures will be performed to ensure safety and compliance with the exercise prescription. After completion of the AT phase, the AT-only group will perform the light chair-based maneuvers described above for 20 min. In contrast, the AT+RT group will go on to the 20 minute RT regimen described below.

Resistance training. Participants in AT+RT will have a short rest period before initiating the RT session. The progressive RT intervention is designed to elicit adaptations resulting in increased skeletal muscle strength, mass, and quality. Participants will exercise in small groups to allow a rotation/rest between machines and enhance the social environment. All participants will first attend an orientation session where correct use of the equipment will be demonstrated. Heart rate, blood pressure, and rhythm will be monitored before and after the RT session.(225) We will use a gradual progression to allow participants to become familiar with the equipment, minimize muscle soreness and reduce potential for injury. We have had excellent safety using this approach.

To optimize the resistance stimulus for maximal functional gain, the exercise prescription is based on a relative intensity level and will progress at a rate specific to each individual's strength gain. The RT regimen is based on AHA and ACSM guidelines for intensity, number of repetitions, number of sets, and frequency.(5; 225) It will consist of 2 upper and 4 lower body exercises on Nautilus RT equipment which can accommodate different body sizes and allow small increments in resistance, both important considerations for low-functioning older HF patients. As employed in studies of HFrEF,(29; 58; 61; 112; 143; 177; 192; 203; 208; 218) the RT exercises (and muscle groups affected) will be: leg curl (hamstrings), leg extension

(quadriceps), leg press (multi-joint: knee extensors and hip flexors), calf raises (gastrocnemius), chest press (pectorals and triceps), and compound row (latissimus dorsi and biceps). For the first 3 weeks, 1 set of 8-12 repetitions will be done on each exercise. To deliver a progressive muscle stimulus, starting at week 4, a second set of each exercise performed to volitional fatigue will be added. Participants will be instructed to complete the concentric phase of the movement in ~2-3 sec, pause briefly at the mid-point, and complete the eccentric phase in ~2-3 sec with ~1-min rest between sets. Using a 2:1 recovery-exercise ratio (1 min recovery after 30 sec RT), the RT (12 total sets of RT exercises) will require ~20 minutes.

The initial resistance (weight) setting on each piece of equipment will be based on the person's one-repetition maximum (1-RM) tested on the machine. The 1-RM testing process is well described(2; 102; 225) and well-tolerated by older adults, including those with HFrEF.(177) During the first 3 weeks, the weight on each exercise will be 20-30% of participants' 1-RM. In addition to adding a 2nd set of each exercise, beginning at week 4, the resistance will increase to 40-50% of 1-RM. For the remaining 20 weeks, if >12 repetitions are completed on the 2nd set in 2 consecutive sessions, the weight will be increased for the next session. The 1-RM testing will be repeated every 4 weeks to assess gains in strength and help ensure optimal resistance settings. The goal will be to achieve 70-80% 1-RM for the last 8 weeks of the study. Amount of weight lifted, number of repetitions, and sets completed for each session will be recorded.(225) Our experience and others' indicate this regimen will produce sufficient stimulus time & load progression to elicit the desired neuromuscular adaptations.(2; 80; 102)

Adherence, retention, and intercurrent illness. We will utilize multiple behavioral management strategies to create a positive exercise environment and ensure compliance, including promptly contacting participants who miss a session, scheduling makeup sessions, and individual counseling sessions with Dr. Brubaker to discuss strategies to promote attendance and limit obstacles to participation. Using these strategies in 3 prior exercise trials in older HFpEF patients, we had excellent attendance (88%) and retention (87-93%). If a participant has a change in health status or intercurrent illness, Dr. Kitzman will communicate with the personal physician to determine suitability for returning to the intervention, and with Dr. Brubaker who will determine need for modifications to the exercise prescription. In prior studies, only 3% of patients had intercurrent illness requiring interruption of the intervention and all but 1% were able to return to complete the study. If there is a substantial change in beta-blocker dosage, we will re-evaluate the heart rate range.

Caloric restriction intervention. The caloric restriction intervention will be supervised by Denise Houston, PhD, RD, Co-I, in coordination with Linda Easter, MS, RD, LDN and conducted in accord with published recommendations for overweight/ obese older adults (213; 221) similar to our recent trial in obese older HFpEF patients. A hypo caloric diet (lunch and supper daily, plus snacks), will be prepared by the CRU Metabolic Kitchen. Portions are weighed individually. Menus will be provided to guide food selection and preparation of daily breakfasts, and participants will be reminded to consume only the items provided and to keep a log. Participants will pick up meals 3 times/week; in addition to this frequent staff contact, there will be weekly weigh-ins and progress review sessions, further ensuring safety. Participants choose from a 36-item menu, enhancing acceptance. We will employ several strategies to enhance compliance including weekly individual counseling sessions if diet records or inadequate weight loss suggest suboptimal compliance and allowance of 2 'free' days/month. We have successfully conducted several weight loss trials in older adults, including our recently completed trial in HFpEF patients and achieved 99% meal compliance, consistent weight loss, with excellent safety and no adverse events.(16; 198)

The diet will be adjusted to achieve a 300 kcal/day deficit. Our preliminary data in this population indicate this is safe and when combined with exercise will produce a total weight loss of ~10.0 kg (about 9.5% body weight) over the 20-week intervention. Individual calorie levels will be prescribed using measured RMR by indirect calorimetry(51) which in our preliminary study yielded an average daily intake of ~1650kcal/day. To further ensure safety, no participant will receive less than 1100 kcal/day for women and 1300kcal/day for men, and total weight loss will be capped at 15% of body weight or a BMI of 25 kg/m^2. The tailored meals provide a balanced diet with <30% calories from fat and 1.2 g protein/kg/day.(13; 79; 162) Overall, participants will receive ~1.5 gm protein/kg/day, ensuring adequate protein intake, consistent with recommendations for older adults undergoing weight loss(26; 55; 134; 154; 222) and the Dietary Reference Intake Standards for Macronutrients.(13; 162) Per PROT-AGE recommendations,(13) patients with eGFR < 30 ml/min/1.73 m^2 will be excluded.

Outcome Measure(s)

All outcomes assessments will be performed at baseline and following the 20-week intervention and will be assessed by observers blinded to intervention group assignment when feasible. Written, informed consent will be obtained from each subject by trained research staff using an IRB-approved consent form and study protocol.

Exercise testing. Exercise tolerance will be measured as peak VO_2. The primary outcome will be determined during a progressive exercise test on a motorized treadmill according to standards established by the American Heart Association and as previously described in detail.(33; 83; 125; 176; 224) The standardized extended modified Naughton protocol will be used which is well suited to older heart failure patients.(75; 227) Expired gases will be measured with a MedGraphics (Minneapolis, MN) Ultima system following calibration for VO_2, VCO_2.(125; 155; 165) Patients will be encouraged to give a maximal, exhaustive effort as judged by either an RER > 1.05 or >90% age predicted maximal heart rate. Blood pressure, heart rate, and ECG will be continuously monitored. The tests will be administered by a Master's-level exercise physiologist, and attended by a cardiologist. We have administered > 800 maximal exercise tests in older heart failure patients in clinical trials without a significant adverse event. VO_2 will be assessed by averaging the final three 15 sec averages, ventilatory threshold by the Wasserman method, and VE/VCO_2 slope as previously described in detail in older patients with HFpEF in our laboratory.(32; 114; 125; 145; 155)

Six-minute walk distance (6MWD). The 6MWD test is a well-established outcome measure in HF. It is valid and reproducible in patients with a wide range of physical function, predicts clinical events, and responds to interventions.(1; 54; 129; 195) We showed that it is as predictive of clinical events as exercise oxygen consumption,(70) and improves with AT, including in older HFpEF patients.(128; 167) The 6MWD will be conducted by the method of Guyatt et al(90) at the first and last visits to the Wake Forest University Clinical Research Center utilizing a standardized script as previously reported.(1; 70; 71) Total distance covered and number and duration of rests and symptoms will be recorded.

Short physical performance battery (SPPB). The SPPB is a measure of physical function that incorporates three components: usual gait speed measured over 4 meters, timed repeated chair rise, and standing balance with progressively narrow base of support. Each component is scored on a 0-4 scale and then summed to provide an overall score range of 0-12. We will evaluate the overall SPPB as well as each component. A change of 1 point in the overall SPPB score has been identified as representing a substantial change and 0.5 points as a small meaningful change.(172)

Lower extremity muscle strength will be assessed as maximal isokinetic knee extensor strength (Newton-meters, Nm) in both legs using an isokinetic dynamometer (Biodex®) with the participant seated and the hips and knee flexed at 90°. For consistency, seat height and depth will be recorded and the best of 2 trials will be selected. Test-retest reliability of knee extensor maximal voluntary contraction is high among older adults.(38; 189)

Hand grip strength will be measured in both hands using an adjustable grip strength dynamometer.(113) The participant will be seated with the elbow at 90 degrees. Two trials will be recorded for each hand.

Body composition will be measured by dual-energy x-ray absorptiometry (DXA, Hologic Delphi QDR).(100) Scans will be analyzed by a certified DXA technician experienced in body composition measures in older adults.(100) Whole body DXA estimates body and regional mass, lean mass, fat mass, and bone. Percent lean mass will be calculated as lean mass / total mass x 100. Total and appendicular skeletal muscle mass will be estimated using the Heymsfield method.(42) Precision of our DXA lean mass measurements is excellent (CV = 0.51%).

Thigh muscle composition will be assessed by MRI on a 3.0 T Skyra scanner (Siemens) as previously described.[1] The left thigh will be scanned using a cardiac phased array coil. A scout view will be obtained by single phase, multi-slice coronal acquisition. The slices will be 10 mm thick with a 5-mm gap, with a 256 x 128 matrix, a 40-cm field of view, a 30° flip angle, an auto repetition time, and a minimum echo time. Images will be transferred to a dedicated image analysis workstation and the slice corresponding to a constant location of the mid-thigh will be selected.(111) Cross-sectional areas of skeletal muscle (SM), intermuscular fat (IMF), and subcutaneous fat (SCF) will be measured using commercially available software (Tomovision, Montreal, Quebec). This technique was been validated against cadaver specimens.(152) Duplicate tests from 10 random subjects analyzed in a blinded fashion yielded correlation coefficients for SM, IMF, and SCF of 0.99, 0.98, and 0.99 respectively, similar to others.(105) We will use fat-water separation by the Dixon method, recently shown to enhance precision of muscle mass measures.(228) DXA provides total lean mass and is widely available; MRI provides regional thigh mass and is independent of fluid fluctuation which could affect DXA measurements.

Muscle quality will be calculated as the ratios of knee extensor strength to thigh muscle area assessed by MRI (Nm/cm^2) and leg lean mass assessed by DXA (Nm/kg lean mass). Muscle quality for the upper extremity will be calculated using dynamometer grip strength and DXA arm lean mass.

Health-related QOL. The Kansas City Cardiomyopathy Questionnaire (KCCQ) is a 23-item self-administered questionnaire that quantifies physical function, symptoms, social function, and self-efficacy in HF patients. It is a well-established survey that is valid and sensitive to physical and psychological effects from HF and its treatment, including with exercise in our previous trials of older HFpEF patients.(66; 68) KCCQ score is an independent predictor of exercise capacity,(66; 67) all-cause mortality, and cardiovascular death and hospitalization,(130) and is more sensitive to change than other QOL measures.(88; 202) In addition, the SF-36, EuroQOL, MOCA and CES-D will be administered.

LV structure / function and arterial function will be assessed by cardiac MRI (CMR) and echo-Doppler as previously described.[12,13,146,231] Although our hypotheses focus on skeletal muscle, assessing the effect of RT on cardiovascular function will allow us to examine safety and

potential benefit. This can be accomplished in the same setting as thigh imaging with a single 30-minute exam, minimizing participant burden and cost. RT can increase LV mass while CR can decrease it; RT can also increase arterial stiffness.(153; 225) CMR is the most sensitive test for changes in LV mass.(108; 158) LV volumes, ejection fraction, and strain, aortic distensibility and left atrial (LA) volume will be measured using a Steady State Free Precession cine protocol(35; 40; 41; 106-108; 118; 138; 163; 216) and body coil.[231] A stack of short axial images of the LV and LA will be obtained.(141) Epicardial / endocardial borders will be traced using a semi-automatic method (QMASS 7.1, Medis) and LV and LA volumes will be calculated by Simpson's rule(25; 118; 163) Circumferential LV strain will be assessed by myocardial tissue tagging(140) and analyzed using the Harmonic Phase technique.(82; 169) Aortic distensibility will be measured using phase-contrast gradient-echo sequences.(39; 106; 109; 118)

Echo-Doppler will be performed with a Phillips iE33 (Andover, MA) instrument according to ASE recommendations, as previously described.(118; 125; 126; 139; 220) Early mitral annulus velocity by tissue Doppler (Ea) reflects diastolic relaxation(161; 204) and ratio of peak early filling velocity (E) to Ea (E/Ea) estimates LA pressure.(159; 204; 206) We've shown these outcomes correlate with peak VO_2, have prognostic value, and respond to interventions.(81) We will assess carotid artery distensibility and carotid-femoral pulse-wave velocity as previously described.(118; 124; 127) Measures will be performed in triplicate by blinded personnel.

Biomarkers: B-type natriuretic peptide, an established biomarker of HF severity and treatment response, will be analyzed on baseline/follow-up frozen plasma using a standardized, commercial radioimmunoassay.(118; 125; 127; 128)

Thigh muscle tissue will be obtained as previously described from the left *vastus lateralis* by percutaneous needle biopsy under local anesthesia using aseptic technique and a 6mm University College Hospital needle and a 60cc syringe for suction. Over 700 muscle biopsies have been performed using this technique in older research participants, including HFpEF, with good tissue yields (161±79 mg, >100 mg in 83%) and no serious complications.(164) The portion intended for immunoblot analyses is harvested and immediately stored at -80°C. The portion intended for respirometry will be processed as described below.

Mitochondrial function will be examined comprehensively by analysis of key aspects of mitochondrial physiology (**Table 2**). Measures for this exploratory aim were selected to be relevant to older, obese patients with HFpEF and the effects of RT.

Mitochondrial Physiology	Table 2. Mitochondrial Outcome Assessments
Respiratory Function	• Respiratory control assessed with complex I, II and β-oxidation specific substrates (isolated mitos) • Respirometric kinetics and OXPHOS efficiency (Permeablized muscle fiber bundles- PmFBs)
Content / Structure / Biogenesis	• Content - citrate synthase activity; Expression of Porin, cardiolipin,Cox4, and Complexes I-V (Western blot); mitochondrial isolation yields • Structure – fiber type, cross-sectional area (histology); Mfn1, Mfn2, MFF, DRP1, Fis1, OPA1 expression (Western blot) • Biogenesis - PGC1α, TFAM, SIRT3 expression (Western blot)
Mitochondrial-Mediated Cell Death	• Bcl-2, Bax, ICE, p53, Fas receptor protein, and Cyclophilin D expression (Western blot) • Susceptibility to calcium-induced mPTP opening (PmFBs) • Mitochondrial H_2O_2 emitting potential (PmFBs)

Muscle biopsy yield in our preliminary studies in HFpEF averaged 138 mg, sufficient for completion of all proposed experiments; 20-30 mg of tissue to isolate mitochondria,(24) 10-15 mg to prepare permeabilized fiber bundles (PmFB)(6), and the remainder (~100 mg) frozen for protein expression/histochemistry.

Mitochondrial Respiratory Function will be assessed in parallel by complementary techniques using isolated mitochondria and PmFBs.(30; 173; 175) Isolated mitochondria (5 μg) will be assessed with the Seahorse Bioscience XF24 system as a higher throughput system to maximize screening for potential defects/changes in respiratory control at key points in the electron transport chain (ETC) or tricarboxylic acid (TCA) cycle as previously described.(209) Basal (state 2), ADP-stimulated (state 3), non-ADP-stimulated (state 4) and maximally uncoupled (+FCCP) respiration will be determined under substrate conditions that distinguish potential dysfunction at the level of (1) the PDH complex (pyruvate/malate) vs (2) the TCA cycle and/or complex I (glutamate/malate), (3) complex II (succinate/rotenone), (4) complex I + II (glutamate/malate/succinate), and (5) β-oxidation (palmitoyl-carnitine). Data will be expressed as O_2 consumption per mg mitochondrial protein. The PmFB approach will be used to determine in greater detail the kinetics of ADP-stimulated respiration (i.e., Km and Vmax) as previously described.(173; 174) High-resolution respirometry (Oroboros Oygraph-2k, Innsbruck Austria) coupled with direct monitoring of ATP synthesis (fluorometrically) will be used to determine OXPHOS efficiency (ATP /O_2 ratio) during respiration supported by glutamate/malate or succinate/rotenone.(87) All data will be expressed per mg dry weight and normalized for mitochondrial content. RCR, a key pre-planned outcome, will be calculated as the ratio of state 3/state 4.(30)

Mitochondrial Content, Structure, and Biogenesis. Mitochondrial content will be assessed by immunoblot (Porin, cardiolipin, and COXIV) and enzyme activity analysis (citrate synthase).(132) Expression of Complex I-V of the ETC will be determined using the MitoProfile human antibody cocktail (Abcam, ab110411). Regulators of mitochondrial biogenesis (PGC1α, TFAM, and SIRT3) and mitochondrial dynamics (Mfn1, Mfn2, MFF, DRP1, Fis1, and OPA1) will be determined by Western blot.(191)

Mitochondrial Mechanisms for Skeletal Muscle Loss, a phenomenon related to reduced peak VO_2 in HFrEF(3) but never examined in HFpEF, will be assessed by using: 1) expression of Bax, ICE, p53, Fas receptor protein, and cyclophilin D as indices of programmed cell death;(171) 2) Bcl-2 as an index of protection against apoptosis; and 3) calcium retention capacity and H_2O_2 emission in PmFBs as indices of susceptibility to opening of the mitochondrial permeability transition pore and mitochondrial failure.(6; 173)

Physical Activity will be assessed using two accelerometers, the Actigraph GT3X+ and the Lifecorder EX. The Actigraph monitor is a small device worn on the non-dominant wrist, and the Lifecorder monitors is a small device worn on the right hip, attached to the waistband. Both monitors assess variables related to physical activity: energy expenditure, steps, and physical activity duration, intensity, and frequency. Participants will wear both devices for 7 continuous days during baseline and follow-up testing to assess changes in physical activity pre to post intervention. There are no risks associated with wearing an activity monitor.

Study visit timeline.

Table 3. Assessment Timeline **Visit code**	SV	BV1	BV2	BV3	Interv.	FV1	FV2	FV3
Activity/assessment **Week number**					0-20			
Informed consent, screening, demographics, echocardiogram/Doppler, dietary interview	X							
Physical exam, medical history, medication review	X					X		
RMR, Blood draw, questionnaires, Exercise test		X				X		
SPPB, Muscle strength, DXA & MRI scans			X				X	
Muscle biopsy				X				X
Randomization and dietary education				X				

Analytical Plan

The trial is a 2-arm, randomized, parallel design to test the effect of adding RT to the regimen of CR+AT shown as most beneficial in our recent trial. Peak VO_2 (ml/min) will be the primary outcome measure using an intention-to-treat analysis. Analyses will be conducted using analysis of covariance (ANCOVA) with baseline peak VO_2, age and gender as predefined covariates. Similar analyses will be done for the secondary outcomes, skeletal muscle mass and mitochondrial function, QOL, and other outcomes. Partial correlation analysis adjusting for age and gender will be done to correlate changes in peak VO_2 with the other key outcomes of interest (muscle mass, mitochondrial function, and QOL).

Data Management

The REDCap (Research Electronic Data Capture) system will be used for this trial; as we have used this system previously, many data entry fields, screens, and data checks are in place.

Human Subjects Protection

Informed Consent

Written informed consent will be obtained from each subject. The study coordinator will obtain informed consent in private examination room. Study staff will give adequate time for the participant to review the consent form and ask questions. Each participant will be given a copy of the signed consent form.

Confidentiality and Privacy

Confidentiality will be protected by collecting only information needed to assess study outcomes, minimizing to the fullest extent possible the collection of any information that could directly identify subjects, and maintaining all study information in a secure manner. To help ensure subject privacy and confidentiality, only a unique study identifier will appear on the data collection form. Any collected patient identifying information corresponding to the unique study identifier will be maintained on a separate master log. The master log will be kept secure, with access limited to designated study personnel. Following data collection subject identifying information will be destroyed at the earliest opportunity, consistent with data validation and study design, producing an anonymous analytical data set. Data access will be limited to study staff. Data and records will be kept locked and secured, with any computer data password protected. No reference to any individual participant will appear in reports, presentations, or publications that may arise from the study.

Data and Safety Monitoring
The principal investigator will be responsible for the overall monitoring of the data and safety of study participants. The principal investigator will be assisted by other members of the study staff. If during the study assessments, an incidental medical finding occurs, the principal investigator will be notified immediately. Findings will also be reported to the patient's personal physician for further determination of appropriate care.

Although a DSMB was not required by NIH because it was deemed a low risk protocol, we have elected to utilize a DSMB for this study, the NIH-supported, Pepper Center DSMB, which successfully monitored the recently completed prior cycle of this project, which had a similar patient population, methods, and intervention. This DSMB monitors all Pepper Center supported projects. These DSMB members have appropriate expertise for this project and are: Curt Furberg, MD (Chair); Paul Laurienti, MD, Jack Rejeski, PhD, Tim Howard, PhD, Douglas Case, PhD. This plan has been approved by Dr. Steve Krichevsky, Director of the Aging Center and PI of the Wake Forest Pepper Center, and by the NIA program project officer and director.

The DSMB will be charged with monitoring study-wide safety and clinical events on a regular basis (semi-annually). In particular, the DSMB will review the following SAE's and the following specific clinical and safety events: death, hospitalization, hospitalization/ observation unit stay lasting less than 24 hours, emergency room visit, urgent clinic visits, and adverse events occurring while the participant is performing the SECRET II intervention (including angina, syncope/presyncope, palpitations, symptomatic hypoglycemia and/or falls), cardiovascular events (including worsening heart failure, acute coronary syndrome, arrhythmia, and stroke), nursing home placement, and injury (or fall).

Reporting of Unanticipated Problems, Adverse Events or Deviations
Any unanticipated problems, serious and unexpected adverse events, deviations or protocol changes will be promptly reported by the principal investigator or designated member of the research team to the IRB and DSMB.

Long-Term Follow-Up Visit
The purpose of this long-term follow-up visit is to examine the long-term level of weight change (maintenance, continued loss, or regain) following a short-term weight-loss intervention and its effect on exercise capacity, physical function, quality of life, and body composition. A long-term follow-up visit will be conducted to assess changes in weight, VO2peak, physical function, quality of life, and body composition. All long-term follow-up visits will take place following the completion of the original study. Further, the visit(s) will take place no sooner than 1 year following study intervention completion in any participant. Therefore, this long-term follow-up visit will occur between 8 months and 4 years following study intervention completion for each participant.
The exercise testing, physical performance battery, health-related quality of life, body composition by DXA, and an MRI will be conducted. In addition, physical activity monitoring, basic vital signs (height, weight, blood pressure) will be collected and a review and update of medical history will be performed to check for any possible or new contraindications to exercise testing. The blood and stool sample will also be collected at this visit.

This visit should take ~2-4 hours. It may be done in 1 or 2 visits, depending on study participant desire.

SECRET II Physical Activity Sub-Study (PASS)-COSMED K5

Background

The results of our Studies Examining Caloric Restriction and Exercise Trial (SECRET I) demonstrate that 20 weeks of moderate intensity aerobic exercise (AE) together with caloric restriction (CR) was safe and efficacious for individuals with heart failure and preserved ejection fraction (HFpEF) [1]. Despite many positive changes, the AE + CR combination resulted in a significant reduction of total muscle mass in these HFpEF patients [1]. Therefore, we are currently examining the benefit of incorporating resistance exercise training (RE) to improve body composition and exercise capacity in participants with HFpEF in the SECRET II study. Moderate intensity AE is generally prescribed at 60-80% of the patient's maximum oxygen consumption (VO_{2peak}) as this level is a safe and effective for HF patients [2]. Since VO_2 cannot be easily measured during AE or RE, heart rate (HR) is commonly used as a surrogate measure to regulate exercise intensity. While previous research has shown that % HR and % VO_{2peak} during AE are well correlated in clinical populations [3], this relationship has not been examined in HFpEF patients. Performing AE at a low intensity (i.e. < 60% VO_{2peak}) may fail to produce optimal physiological benefits, whereas performing AE at an intensity that is too high (i.e. > 80% VO_{2peak}) may be intolerable and potentially dangerous to these HFpEF patients. Thus, it is important to ensure that HFpEF patients are performing AE and RT in the proper range of their % VO_{2peak} to ensure their safety and to stimulate maximal physiological benefits.

Measuring VO_2 during ambulatory AE or RT was not possible until the development of the portable COSMED K5 system (see photo below). This COSMED K5 system, obtained by the Health and Exercise Science (HES) department in 2016, can be used to measure VO_2 outside of the lab environment, while patients are performing their normal activities, and/or AE and RE. This will be the first time such a measurement/study will be performed in HFpEF patients.

In addition to examining the relationship between % VO2 and % HR during AE and RE in HFpEF patients, the COSMED K5 allows for the direct determination of energy expenditure (i.e kcals). In addition to measuring the energy expenditure (in kcals) during AE, we can also determine the additional energy expenditure associated with preforming RE in these HFpEF patients. It's unknown if adding RE to AE will result in a significant increase in energy expenditure versus AE alone in HFpEF patients. These findings will have important implications for weight loss and body composition changes and have not been assessed in HFpEF patients.

Based on existing literature and direct experience we developed the following hypotheses;

1. The average % HR <u>will not be</u> significantly different that the average % VO_{2peak} during either the AT only or AT + RT sessions.
2. The average physical activity energy expenditure (PAEE) during a typical exercise session AT or AT + RT <u>will be</u> significantly less than the recommended 300 kcal/day.
3. AT + RT <u>will</u> result in significantly higher PAEE than AT alone.

Methods.

This research project would be conducted in HF patients that are already participating in the SECRET II study funded by the NIH and approved by WFUBMC IRB. Participants in SECRET II are randomly assigned to two groups; CR + AE or CR+AE+RE. The SECRET II intervention is 20 weeks and will eventually enroll up to 90 HF patients over a 4 year period. This proposed sub-study would be conducted on 15-20 of the HFpEF patients already performing AE with/without RE in SECRET II study. All data collection for this sub-study would take place at the Health and Exercise Science Department's Clinical Research Center under the supervision of Dr. Brubaker and will be stored on encrypted computers and/or in locked files/offices.

Participants in SECRET II would be asked to voluntarily participate in two experimental sessions (one near the beginning and one near the end of their 20 week intervention). For each session the participants would wear the portable COSMED K5 system while performing their normal AE $\pm$ RE exercise session. Expired air will be collected continuously during the entire exercise session that lasts ~ 1 hr. From the expired air collected by the COSMED K5 mask, the VO_2 for each minute will be obtained and compared to HR values that are obtained from a wrist worn heart rate monitor (see photo below). This data would allow us to determine if these HFpEF patients are at the appropriate intensity levels during AE $\pm$ RE.

Furthermore, since we will be able quantify the physical activity energy expenditure (PAEE measured in kcal) from the VO_2 values obtained during both AE and AE + RE, we can compare the two groups to determine if there are additional metabolic costs associated with RT. Finally, to determine the reliability of these measures (VO_2, HR, and kcal) we will ask the first 5 participants in the study to perform a second identical experimental session ~ 1 week after the first session.

Risks.

There are no additional risks, beyond those associated with AE and RE, for the volunteers in this sub-study. Volunteering participants will perform their "normal" AE $\pm$ RE session as part of SECRET II while wearing the COSMED K5 mask. This mask comfortably covers the subject's mouth/nose and allows, through a one-way valve system, for normal inhalation of room air and expiration to the analyzer. If at any point the mask becomes uncomfortable to the participant, it will be removed and the experimental session will be terminated. This is the same mask the participant wears during their baseline exercise test so they will already be familiar with it.

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COSMED K5

Garmen HR monitor

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