Original Investigation

Effect of Caloric Restriction or Aerobic Exercise Training on Peak Oxygen Consumption and Quality of Life in Obese Older Patients With Heart Failure With Preserved Ejection Fraction
A Randomized Clinical Trial

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IMPORTANCE More than 80% of patients with heart failure with preserved ejection fraction (HFPEF), the most common form of heart failure among older persons, are overweight or obese. Exercise intolerance is the primary symptom of chronic HFPEF and a major determinant of reduced quality of life (QOL).

OBJECTIVE To determine whether caloric restriction (diet) or aerobic exercise training (exercise) improves exercise capacity and QOL in obese older patients with HFPEF.

DESIGN, SETTING, AND PARTICIPANTS Randomized, attention-controlled, 2 × 2 factorial trial conducted from February 2009 through November 2014 in an urban academic medical center. Of 577 initially screened participants, 100 older obese participants (mean [SD]: age, 67 years [5]; body mass index, 39.3 [5.6]) with chronic, stable HFPEF were enrolled (366 excluded by inclusion and exclusion criteria, 31 for other reasons, and 80 declined participation).

INTERVENTIONS Twenty weeks of diet, exercise, or both; attention control consisted of telephone calls every 2 weeks.

MAIN OUTCOMES AND MEASURES Exercise capacity measured as peak oxygen consumption ($\dot{V}O_2$, mL/kg/min; co-primary outcome) and QOL measured by the Minnesota Living with Heart Failure (MLHF) Questionnaire (score range: 0–105, higher scores indicate worse heart failure–related QOL; co-primary outcome).

RESULTS Of the 100 enrolled participants, 26 participants were randomized to exercise; 24 to diet; 25 to exercise + diet; 25 to control. Of these, 92 participants completed the trial. Exercise attendance was 84% (SD, 14%) and diet adherence was 99% (SD, 1%). By main effects analysis, peak $\dot{V}O_2$ was increased significantly by both interventions: exercise, 1.2 mL/kg body mass/min (95% CI, 0.7 to 1.7), $P < .001$; diet, 1.3 mL/kg body mass/min (95% CI, 0.8 to 1.8), $P < .001$. The combination of exercise + diet was additive (complementary) for peak $\dot{V}O_2$ (joint effect, 2.5 mL/kg/min). There was no statistically significant change in MLHF total score with exercise and with diet (main effect: exercise, −1 unit [95% CI, −8 to 5], $P = .70$; diet, −6 units [95% CI, −12 to 1], $P = .08$). The change in peak $\dot{V}O_2$ was positively correlated with the change in percent lean body mass ($r = 0.32$; $P = .003$) and the change in thigh muscle:intermuscular fat ratio ($r = 0.27$; $P = .02$). There were no study-related serious adverse events. Body weight decreased by 7% (7 kg [SD, 1]) in the diet group, 3% (4 kg [SD, 1]) in the exercise group, 10% (11 kg [SD, 1] in the exercise + diet group, and 1% (1 kg [SD, 1]) in the control group.

CONCLUSIONS AND RELEVANCE Among obese older patients with clinically stable HFPEF, caloric restriction or aerobic exercise training increased peak $\dot{V}O_2$, and the effects may be additive. Neither intervention had a significant effect on quality of life as measured by the MLHF Questionnaire.

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Heart failure with preserved ejection fraction (HFPEF) is the most rapidly increasing form of heart failure, occurs primarily in older women, and is associated with high rates of morbidity, mortality, and health care expenditures.[1] However, its pathophysiology is poorly understood, and medication trials to date have been neutral.

Most previous HFPEF trials focused on mediating the long-term consequences of hypertension. However, obesity is also an independent risk factor for development of heart failure,[2,3] and more than 80% of patients with HFPEF are overweight or obese.[4,5] Increased adiposity promotes inflammation, hypertension, insulin resistance, and dyslipidemia and impairs cardiac, arterial, skeletal muscle, and physical function;[6-8] all of which are common in HFPEF and contribute to its pathophysiology.[9] It was recently shown that the severity of exercise intolerance, the primary symptom and major contributor to reduced quality of life (QOL) in patients with chronic HFPEF, is significantly correlated with increased body adiposity and skeletal muscle adipose infiltration.[6,10]

DXA *dual x-ray absorptiometry*

HFPEF *heart failure with preserved ejection fraction*

QOL *quality of life*

SM:IMF *skeletal muscle: intermuscular fat ratio*

In obese older individuals without heart failure, weight loss via dietary caloric restriction (diet) improves left ventricular hypertrophy and diastolic function; exercise capacity; glucose, lipid, and blood pressure control; inflammation markers; body composition; and skeletal muscle function.[8,11-13] However, diet is controversial in patients with heart failure; observational studies suggest overweight or mildly to moderately obese patients with heart failure (including HFPEF specifically) survive longer than those who are normal weight or underweight.[5] There have been no studies of diet in any type of heart failure and current HFPEF management guidelines do not include diet.[14]

The objective of this study was to conduct a randomized, single-blind, attention-controlled trial to examine the effects of diet, alone and combined with aerobic exercise training (exercise), on exercise capacity measured as peak exercise oxygen consumption per unit time ($\dot{V}O_2$, co-primary outcome) and QOL (co-primary outcome), and exploratory outcomes of body composition, leg muscle function, cardiac function, and inflammation in obese older patients with HFPEF.

Methods

The trial was conducted at Wake Forest School of Medicine from February 2009 through November 2014, approved by the institutional review board, and registered. Participants provided written informed consent.

Study Participants

Participants were identified from search lists of medical records.[15,16] Inclusion criteria for participants were 60 years or older; body mass index (BMI; calculated as weight in kilograms divided by height in meters squared) of 30 or higher; symptoms and signs of heart failure defined by the National Health and Nutrition Examination Survey Congestive Heart Failure criteria score of 3 or higher[17] or the criteria of Rich et al,[18] or both; and left ventricular ejection fraction of 50% or more. Major exclusion criteria were left ventricular segmental wall motion abnormalities and significant ischemic or valvular heart disease, pulmonary disease, anemia, or other disorder that could explain the participants' heart failure symptoms. Participants were clinically stable, had no significant change in cardiac medications for 4 weeks, and were not undergoing regular exercise or diet.

Outcomes

Co–Primary Outcomes

Cardiopulmonary exercise testing was performed on a motorized treadmill using the modified Naughton protocol to the end point of exhaustion.[19] Gas exchange was measured continuously during exercise (Ultima, Medical Graphics). Peak $\dot{V}O_2$ (mL/kg body mass/min), the co-primary outcome, was the average of measures from the last 30 seconds during peak exercise.[19]

The other co-primary outcome was disease-specific QOL assessed as the total score from the Minnesota Living with Heart Failure (MLHF) Questionnaire.[16,17,20] The MLHF score range is 0 through 105, higher scores indicate worse heart failure–related QOL.

Exploratory Outcomes

Exercise time, 6-minute walk distance, ventilatory anaerobic threshold, and ventilation/carbon dioxide output slope were assessed as previously described.[15,19]

Total body lean mass and fat mass were measured by dual energy x-ray absorptiometry (DXA; Hologic) according to standardized protocols.[10] Thigh muscle and fat areas and abdominal, epicardial, and pericardial fat areas were measured using magnetic resonance imaging (MRI), and an image analysis workstation (TomoVision), version 2.1.[6]

Leg press power (measured in W) was assessed using the Nottingham power rig. Muscle quality was calculated as leg power divided by thigh muscle area (W/cm^2) from MRI.

Heart failure–specific QOL was assessed with the Kansas City Cardiomyopathy Questionnaire (KCCQ; range 0-100; higher scores indicate better QOL) and general QOL was assessed with the 36-item Short-Form Health Survey (SF-36) physical component score (range 0-100, the average is 50 and higher scores indicate better QOL).[15,16,21,22]

Doppler echocardiograms were performed and analyzed per American Society of Echocardiography recommendations.[16] Doppler left ventricular filling patterns and pulse-wave velocity were assessed as described.[16]

Left ventricular mass and volumes were assessed by cardiac MRI from multislice, multiphase gradient-echo sequences that were traced manually and calculated by summation.

Blood was collected after overnight fasting and stored at −80°C. B-type natriuretic peptide (BNP) was measured by radioimmunoassay (Phoenix Pharmaceuticals).[15,23] High-sensitivity C-reactive protein and plasma interleukin 6 were measured by enzyme-linked immunosorbent assays (eMethods in the Supplement).

Blinding of Outcomes Assessments

The principal investigator and all study investigators, except the biostatistician, were blinded to all study outcomes. Personnel performing the outcome measures were blinded to participant group. For practical considerations, an exception was for cardiopulmonary exercise testing, for which the supervising physician and staff were blinded to the baseline (prerandomization) results. To minimize bias, standardized procedures known to elicit maximal exercise performance were used, including a standardized protocol, guidance by the respiratory exchange ratio (RER, an objective indicator of effort) and Borg scale of perceived exertion, and reading of a standardized participant instruction script prior to each exercise test.

Randomization

After baseline assessments were completed, participants were randomized using a computer-generated list using SAS software (SAS Institute), version 9.0, maintained by the study statistician and stratified by β-blocker medication and sex to 1 of 4 groups consisting of exercise only, diet only, combined exercise and diet (exercise + diet), or attention control (control). No blocking across time was used.

Interventions

Participants randomized to either group receiving exercise completed 1-hour supervised exercise sessions 3 times per week for 20 weeks consisting primarily of walking exercise using an individualized exercise prescription based on the exercise test results, and intensity level was progressed as tolerated and based primarily on heart rate reserve.[15,16]

Participants randomized to either group receiving diet were prescribed a hypocaloric diet using meals (lunch, dinner, and snacks) prepared by the Wake Forest University General Clinical Research Center metabolic kitchen under direction of a registered dietitian. Participants prepared their own breakfast from a menu. Individual energy needs were calculated from resting metabolic rate (CCM Express, MGC Diagnostics) following an overnight fast and an activity factor based on self-reported daily activity. Prescribed calorie intake deficits were approximately 400 kcal/d for the diet group and approximately 350 kcal/d for the exercise + diet group (the difference between the groups allowed for the energy expenditure of the exercise intervention), but not less than 1000 kcal/d. The diet provided approximately 1.2 g of protein/kg ideal body weight, 25% to 30% fat calories, and the remainder as carbohydrate. Participants were provided daily calcium supplements (600 mg) and kept records of all food consumed, which was monitored weekly.

Participants randomized to control received neither diet nor exercise interventions and voluntarily agreed to not make diet or exercise changes during the 20-week study. They received telephone calls every 2 weeks from staff in an attempt to match that received by participants in the diet and exercise groups.

Statistical Analysis

All analyses were performed with SAS (SAS Institute), version 9.0. The study was a 2 × 2 factorial design to estimate the main effect of the 2 interventions, exercise and diet, and the primary and exploratory outcomes were tested at the 5% 2-sided level of significance. The trial was designed to have 2 co-primary outcomes, the performance measure peak $\dot{V}O_2$ (mL/kg/min) and the MLHF questionnaire total score. All available outcome data were analyzed in an intention-to-treat analysis. The analysis testing the main effects of diet and exercise and their interaction was performed using analysis of covariance with the baseline measure of the outcome measure, sex, and β-blocker usage as covariates. This method adjusts for differences in the means of the baseline measure of the outcome and other predictor covariates to estimate what the mean in each level of the factor would be had both groups had the same overall mean of the covariates in the model. This method is equivalent to multiple imputation of missing data with the covariates as predictors and infinite iterations. We also performed sensitivity analyses to assess the effect of missing data. The least squares means were presented along with either the standard error or 95% CI. The main effect of each intervention, which is the difference in the LS means between the 2 levels of each of the factors (exercise and diet) is presented along with its 95% CI and a *P* value. Based on a previous study of participants with heart failure, sample size calculations indicated that 80 evaluable participants would provide more than 80% power to detect a main effect of 6% in peak $\dot{V}O_2$ and effect size of 20% on MLHF total score. Allowing for up to 20% loss to follow-up, 100 participants were randomized to the 4 groups. Because the test for interaction between the 2 factors, which is a linear contrast between the 4 individual group means, has low power, the 2 interventions were considered additive (complementary) only if the *P* value for intervention was .10 or lower.

Baseline participant characteristics are presented as mean and standard deviation or frequency and percent. Associations between changes in exercise capacity and other variables were made by Pearson correlations.[19]

See the Supplement for additional details on sample size, effect size, testing for interaction, multiple comparisons, multiple stepwise regression, and missing data.

Results

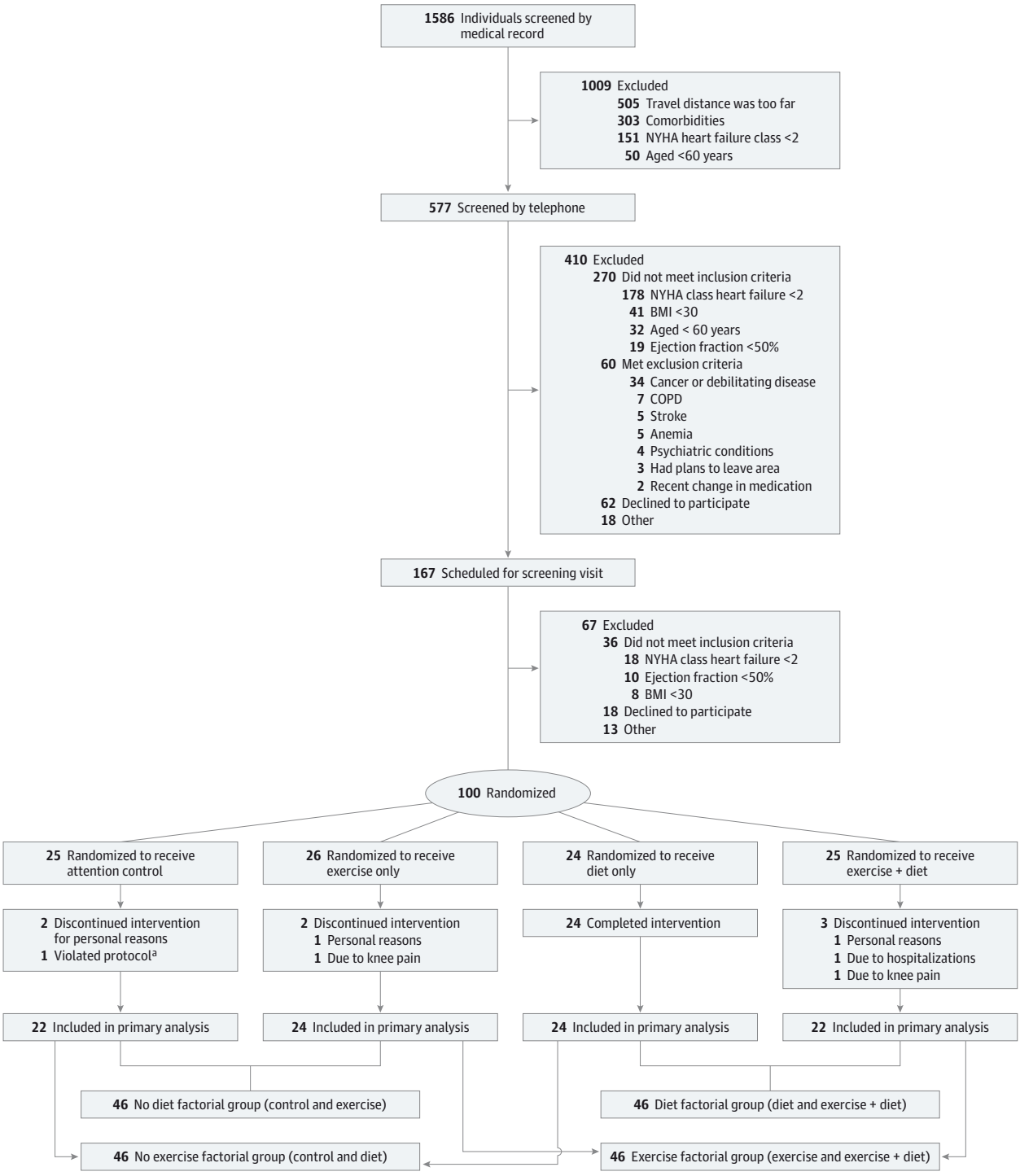
Participants

From 1586 records reviewed, 577 participants were further screened by telephone; 167 were scheduled for a screening visit. Ultimately, 100 participants with HFPEF (mean [SD]: age, 67 years [5]; BMI, 39.3 [5.6]) were enrolled and randomized: exercise, 26; diet, 24; exercise + diet, 25; control, 25 (**Figure 1**). Of these, 92 participants (exercise, 24; diet, 24; exercise + diet, 22; control, 22) completed the intervention and follow-up testing (Figure 1). Participant characteristics were generally in accord with those observed in population studies, with predominantly women (n = 81) and high rates of hypertension, diabetes, left ventricular hypertrophy, and diastolic dysfunction (**Table 1**).

Primary Outcomes

Both diet and exercise significantly increased exercise capacity as determined by the co-primary outcome, peak $\dot{V}O_2$ (main

Figure 1. Flow of Participants Through the Study



BMI indicates body mass index (calculated as weight in kilograms divided by height in meters squared); COPD, chronic obstructive pulmonary disease; NYHA, New York Heart Association.

[a] Violated protocol by immediately undertaking formal, aggressive diet and exercise interventions outside of protocol.

effect: diet, 1.3 mL/kg body mass/min [95% CI, 0.8 to 1.8]), $P < .001$; exercise, 1.2 mL/kg body mass/min [95% CI, 0.7 to 1.7], $P < .001$). Diet and exercise were additive (complementary) and together produced an increase in peak $\dot{V}O_2$ of 2.5 mL/kg/min.

The co-primary measure of QOL as measured by the MLHF total score was not significantly different with exercise and with diet (main effect: exercise, −1 unit [−8 to 5], $P = .70$; diet, −6 units [−12 to 1], $P = .08$) (**Figure 2**) (**Table 2**).

Table 1. Baseline Characteristics of Factorial Groups at Randomization

Characteristic	Factorial Group, mean (SD)			
	Exercise (n = 51)	No Exercise (n = 49)	Diet (n = 49)	No Diet (n = 51)
Demographic and Weight Characteristics, Mean (SD)				
Age, y	66.9 (5.5)	66.0 (4.8)	66.4 (5.0)	66.6 (5.4)
Women, No. (%)	41 (80)	40 (82)	40 (82)	41 (80)
White, No. (%)	28 (55)	27 (55)	24 (49)	31 (61)
Body weight, kg	109 (21)	102 (13)	105 (17)	106 (19)
Body surface area, m^2	2.12 (0.22)	2.06 (0.15)	2.09 (0.19)	2.09 (0.19)
BMI	40.3 (7.1)	38.4 (4.8)	39.0 (5.0)	39.7 (7.1)
Body fat, %	45 (6)	46 (7)	45 (6)	45 (7)
Cardiovascular Measures, Comorbidities, and Medications, Mean (SD)				
NYHA heart failure class, No. (%)				
II	27 (53)	33 (67)	31 (63)	29 (57)
III	24 (47)	16 (33)	18 (37)	22 (43)
Ejection fraction, %	60 (6)	62 (6)	61 (6)	62 (6)
Left ventricular mass, g	213 (63)	216 (57)	218 (62)	210 (58)
Relative wall thickness	0.57 (0.12)	0.57 (0.12)	0.56 (0.13)	0.58 (0.11)
Diastolic filling pattern, No. (%)[a]				
Normal	1 (2)	1 (2)	1 (2)	1 (2)
Impaired relaxation	45 (88)	42 (88)	42 (88)	45 (88)
Pseudonormal	5 (10)	4 (8)	5 (10)	4 (8)
Restrictive	0 (0)	1 (2)	0 (0)	1 (2)
e', cm/s	6.3 (1.4)	6.1 (1.6)	6.2 (1.7)	6.2 (1.3)
E/e' ratio	12.9 (3.4)	13.4 (4.0)	13.0 (3.9	13.2 (3.5
B-type natriuretic peptide, median (IQR), pg/mL	24.9 (19.2-39.4)	21.6 (18.2-26.5)	22.0 (19.1-33.0)	22.2 (18.7-33.6)
Current atrial fibrillation, No. (%)	1 (2)	1 (2)	1 (2)	1 (2)
History of diabetes mellitus, No. (%)	21 (41)	14 (29)	16 (33)	19 (37)
History of hypertension, No. (%)	48 (94)	47 (96)	46 (94)	49 (96)
Blood pressure, mm Hg				
Systolic	137 (16)	135 (16)	136 (15)	136 (16)
Diastolic	78 (9)	77 (7)	78 (9)	78 (7)
Current medications, No (%)				
ACE inhibitors	20 (39)	17 (35)	18 (37)	19 (37)
Diuretics	38 (75)	38 (78)	35 (71)	41 (80)
β-Blockers	20 (39)	20 (41)	19 (39)	21 (41)
Calcium antagonists	18 (35)	17 (35)	18 (37)	17 (33)
Nitrates	3 (6)	6 (12)	4 (8)	5 (10)
Angiotensin receptor blockers	19 (37)	16 (33)	15 (31)	20 (39)
Exercise Capacity, Mean (SD)				
Peak $\dot{V}O_2$				
mL/kg/min	14.5 (2.9)	14.5 (2.3)	14.7 (2.9)	14.3 (2.3)
% predicted[b]	58.1 (11.5)	57.9 (9.2)	58.9 (11.5)	57.1 (9.2)
mL/min	1556 (347)	1465 (268)	1533 (346)	1491 (279)
Peak RER	1.12 (0.08)	1.12 (0.10)	1.13 (0.09)	1.11 (0.08)
Exercise time, min	10.0 (2.6)	10.3 (2.1)	10.3 (2.4)	9.9 (2.3)
6-min walk distance				
ft	1337 (270)	1368 (201)	1359 (234)	1346 (245)
% predicted[b]	72.4 (14.6)	74.1 (10.9)	73.6 (12.7)	72.9 (13.2)

Abbreviations: ACE, angiotensin-converting enzyme; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); E, E-wave velocity; e', early mitral annulus velocity (septal); IQR, interquartile range, NYHA, New York Heart Association; RER, respiratory exchange ratio.

Conversion factor: 1 foot is equal to 3 meters.

[a] Diastolic filling pattern determined according to American Society of Echocardiography criteria. The diastolic filling pattern was not evaluable in 1 patient each in the no exercise group and the diet group.

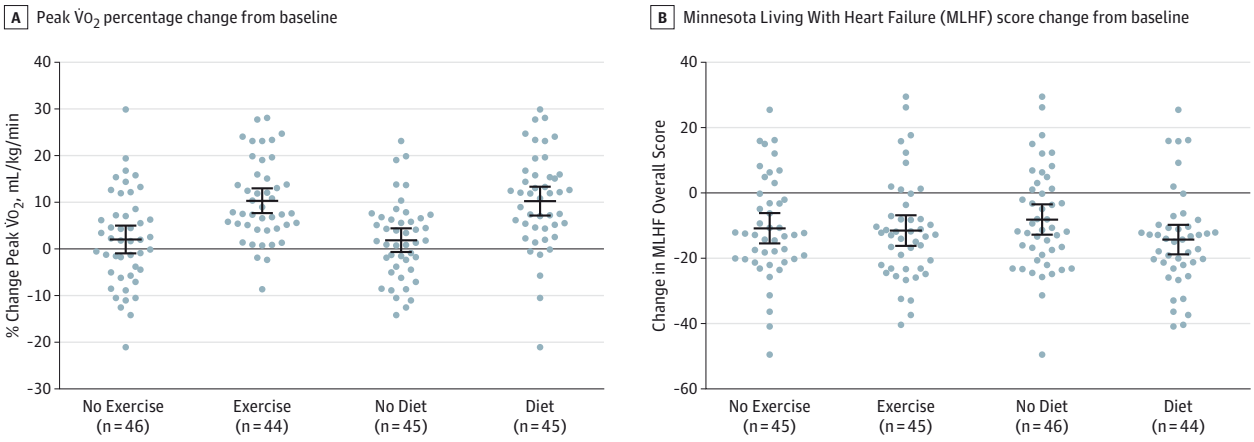
[b] As compared with 60 healthy age and sex-matched sedentary controls.[24]

Exploratory Measures

Exercise Performance

By main effects analysis, both diet and exercise significantly increased multiple other measures of exercise capacity as determined by peak $\dot{V}O_2$ expressed in mL/kg lean body mass/min (exercise, 2.1 [95% CI, 1.0 to 3.1], P = .002; diet, 1.36 [95% CI, 0.2 to 2.3], P = .03) by DXA, in mL/kg lean leg mass/min (exercise, 6.2 [95% CI, 2.7 to 9.7], P = .008; diet, 4.5

Figure 2. Adjusted Individual Changes of Primary Study Outcomes From Baseline to 20-Week Follow-up by Factorial Group



MLHF score has a range from 0 to 105; a higher score indicates worse heart failure–related quality of life. The *P* values represent comparison of least squares means of the outcome measure following adjustment for baseline values, sex, and β-blocker use. The *P* values in panel A were <.001 for each group (exercise vs no exercise; diet vs no diet); in panel B, .70 for the exercise group vs no exercise group and .08 for the diet group vs no diet group. By factorial group, peak $\dot{V}O_2$ data are missing in 4 cases: 2 in the exercise group (due to gas leak and injury), 1 in the diet group (due to injury), and 1 in the no diet group (due to gas leak). By factorial group, MLHF data are missing in 4 cases: 2 in the diet group, 1 in the exercise group, and 1 in the no exercise group (all due to patient errors). Error bars indicate 95% CI and the horizontal bar indicates the mean.

[95% CI, 0.9 to 8.0], *P* = .01), and by MRI in mL/cm^2 thigh muscle area/min (exercise, 1.1 [95% CI, 0.7 to 1.5], *P* < .001; diet, 0.6 [95% CI, 0.2 to 1.1], *P* = .002), as well as $\dot{V}O_2$ reserve (peak minus rest; exercise, 97 mL/min [95% CI, 44 to 141], *P* = .005; diet, 59 mL/min [95% CI, 6 to 113], *P* = .30), exercise time to exhaustion (exercise, 2.0 min [95% CI, 1.4 to 2.6] , *P* < .001; diet, 1.6 min [95% CI, 1.0 to 2.2], *P* < .001), peak workload (measured in metabolic equivalents [METs]; exercise, 0.8 MET [95% CI, 0.4 to 1.1], *P* < .001; diet, 0.7 MET [95% CI, 0.4 to 1.1], *P* < .001), and 6-minute walk distance (exercise, 32.9 m [95% CI, 18.2 to 46.3], *P* < .001; diet, 25.9 m [95% CI, 11.9 to 40.2], *P* = .005) (Table 2). Mean peak RER values were more than 1.10 for all groups at baseline and follow-up, suggesting exhaustive effort. There was an exercise × diet super-additive (synergistic) interaction for 6-minute walk distance (*P* = .09). There were no other significant exercise × diet interactions (Table 2), suggesting the interventions were additive (complementary) for other variables. With diet, muscle quality significantly improved (main effect, 0.15 W/cm^2 [95% CI, 0.03 to 0.27]) but leg press power did not significantly change (main effect, 11 W (95% CI, −2 to 23), *P* = .09) (Table 2).

Measures of QOL

Diet but not exercise significantly improved the KCCQ score, a heart failure–specific QOL measure, by 7 units (95% CI, 2.6 to 12.3; *P* = .004), substantially greater than the accepted threshold (5 units) for clinical relevance (Table 2).[21] Diet also significantly improved the general QOL SF-36 physical component score (diet main effect, 4 units [95% CI, 1 to 7], *P* = .02) (Table 2). There were no significant exercise × diet interactions.

Weight and Body Composition

Body weight was significantly decreased by both diet and exercise (**Table 3**; eFigure 2 in the Supplement) (main effect: exercise, −3 kg [95% CI, −5 to −1], *P* < .001; diet, −7 kg [95% CI, −9 to −5], *P* < .001). With diet main effect analysis, the DXA measures of lean body mass (−2 kg [95% CI, −3 to −1], *P* < .001), fat mass (−5 kg [95% CI, −6 to −4], *P* < .001), and percentage of fat mass (−2% [95% CI, −3% to −1%], *P* < .001) were significantly decreased whereas percentage of lean body mass was significantly increased (2% [95% CI, 1% to 3%], *P* < .001); in contrast with exercise only, fat mass was decreased (−2 kg [95% CI, −3 to −1], *P* = .001) (Table 3). With diet main effect analysis, MRI measures of thigh subcutaneous fat (−16 cm^2 [95% CI, −22 to −10], *P* < .001), thigh muscle (−6 cm^2 [95% CI, −9 to −3], *P* < .001), abdominal subcutaneous fat (−5 cm^2 [95% CI, −20 to 11], *P* < .001), and visceral fat were significantly decreased (−31 cm^2 [95% CI, −43 to −19], *P* < .001) (Table 3); there were no significant changes with exercise. There was no change in pericardial or epicardial fat. There were no significant exercise × diet interactions (Table 3).

Cardiovascular Function

With diet main effect analysis, left ventricular mass by MRI (−4 g [95% CI, −7 to 0], *P* = .03) and left ventricular relative wall thickness by echocardiography (−0.03 [95% CI, −0.05 to −0.01], *P* = .005) were significantly decreased and mitral E/A velocity ratio (0.10 [95% CI, 0.02 to 0.17], *P* = .01) was significantly increased (Table 3). No other cardiac MRI or Doppler echocardiography measure was significantly changed (Table 3; eTable 3 in the Supplement). Arterial pulse-wave velocity was unchanged by either diet or exercise (Table 3).

Symptoms

With both diet and exercise, New York Heart Association symptom class significantly improved (main effect: exercise, −0.4 class [95% CI, −0.6 to −0.2], *P* < .001; diet, −0.4 class [−0.5 to −0.2], *P* = .001) (Table 2).

Table 2. Primary and Secondary Outcomes by Diet and Exercise Factorial Groups

Variable	Overall Baseline, Mean (SD)	Exercise Factorial Groups				Diet Factorial Groups				*P* Value for Interaction Between Exercise and Diet
		Least Squares Mean (95% CI)[a]		Exercise Main Effect, Difference (95% CI)	*P* Value[b]	Least Squares Mean (95% CI)[a]		Diet Main Effect, Difference (95% CI)	*P* Value[b]	
		Exercise (n = 46)	No Exercise (n = 46)			Diet (n = 46)	No Diet (n = 46)			
Primary Outcomes										
Peak $\dot{V}O_2$, mL/kg/min	14.5 (2.6)	16.0 (15.6 to 16.4)	14.8 (14.4 to 15.2)	1.2 (0.7 to 1.7)	<.001	16.1 (15.7 to 16.5)	14.8 (14.4 to 15.2)	1.3 (0.8 to 1.8)	<.001	.67
MLHF Questionnaire score[c]	29 (20)	18 (14 to 22)	19 (15 to 23)	−1 (−8 to 5)	.70	16 (12 to 20)	21 (17 to 25)	−6 (−12 to 1)	.08	.54
Secondary and Exploratory Outcomes										
Exercise performance										
Peak $\dot{V}O_2$										
mL/kg lean body mass/min[d]	28.0 (4.3)	30.3 (29.5 to 31.1)	28.2 (27.4 to 29.0)	2.1 (1.0 to 3.1)	<.001	29.7 (28.9 to 30.5)	28.5 (27.7 to 29.3)	1.3 (0.2 to 2.3)	.03	.25
mL/kg leg lean/min[d]	88.5 (15.4)	95.3 (92.8 to 97.8)	89.1 (86.7 to 91.5)	6.2 (2.7 to 9.7)	<.001	94.0 (91.6 to 96.4)	89.5 (87.0 to 92.0)	4.5 (0.9 to 8.0)	.01	.75
mL/cm^2 muscle/min[d]	12.7 (2.2)	13.8 (13.6 to 14.0)	12.7 (12.5 to 12.9)	1.1 (0.7 to 1.5)	<.001	13.6 (13.4 to 13.8)	12.9 (12.5 to 13.3)	0.6 (0.2 to 1.1)	.002	.15
mL/min	1515 (321)	1575 (1544 to 1606)	1483 (1452 to 1514)	91 (46 to 137)	<.001	1537 (1506 to 1568)	1519 (1488 to 1550)	18 (−27 to 64)	.44	.42
$\dot{V}O_2$ reserve, mL/min	1164 (289)	1257 (1220 to 1294)	1160 (1123 to 1197)	97 (44 to 151)	<.001	1238 (1201 to 1275)	1178 (1141 to 1215)	59 (6 to 113)	.03	.48
Exercise time, min	10.2 (2.4)	12.9 (12.5 to 13.3)	10.9 (10.5 to 11.3)	2.0 (1.4 to 2.6)	<.001	12.7 (12.3 to 13.1)	11.1 (10.7 to 11.5)	1.6 (1.0 to 2.2)	<.001	.53
Workload, MET	5.8 (1.2)	7.1 (6.9 to 7.3)	6.3 (6.1 to 6.5)	0.8 (0.4 to 1.1)	<.001	7.1 (6.9 to 7.3)	6.3 (6.1 to 6.5)	0.7 (0.4 to 1.1)	<.001	.58
Peak heart rate, beats/min	139 (18)	136 (134 to 138)	136 (134 to 138)	0 (−4 to 4)	.90	136 (134 to 138)	136 (134 to 138)	0 (−4 to 4)	.96	.49
Peak blood pressure, mm Hg										
Systolic	178 (19)	171 (167 to 175)	171 (167 to 175)	0 (−6 to 5)	.92	171 (167 to 175)	172 (168 to 176)	−1 (−7 to 5)	.70	.40
Diastolic	78 (9)	73 (71 to 75)	77 (75 to 79)	−4 (−7 to −1)	.005	73 (71 to 75)	78 (76 to 80)	−5 (−8 to −2)	<.001	.54
Peak RER	1.12 (0.08)	1.15 (1.13 to 1.17)	1.12 (1.10 to 1.14)	0.02 (0 to 0.05)	.06	1.15 (1.13 to 1.17)	1.12 (1.10 to 1.14)	0.03 (0 to 0.06)	.048	.52
VAT, mL/kg/min	9.7 (1.9)	10.3 (9.9 to 10.7)	9.8 (9.4 to 10.2)	0.5 (−0.1 to 1.0)	.097	10.2 (9.8 to 10.6)	9.9 (9.5 to 10.3)	0.3 (−0.3 to 0.8)	.34	.88
VE/$\dot{V}CO_2$ slope	29.6 (3.9	29.2 (28.4 to 30.0)	29.6 (28.8 to 30.4)	−0.4 (−1.6 to 0.7)	.43	29.4 (28.6 to 30.2)	29.5 (28.7 to 30.3)	−0.1 (−1.3 to 1.0)	.82	.44
6-min walk, ft	1351 (226)	1503 (1470 to 1536)	1397 (1366 to 1428)	106 (60 to 152)	<.001	1488 (1457 to 1519)	1403 (1370 to 1436)	85 (39 to 132)	<.001	.09
Leg power, W	111 (51)	116 (108 to 124)	118 (110 to 126)	−2 (−14 to 10)	.76	122 (114 to 130)	112 (104 to 120)	11 (−2 to 23)	.09	.71
Leg muscle quality, W/cm^2[e]	0.90 (0.32)	0.97 (0.89 to 1.05)	1.00 (0.92 to 1.08)	−0.03 (−0.15 to 0.09)	.64	1.06 (0.98 to 1.14)	0.91 (0.83 to 0.99)	0.15 (0.03 to 0.27)	.02	.57
Quality of life										
KCCQ score[f]	62 (16)	75 (71 to 79)	73 (69 to 77)	2 (−3 to 7)	.43	78 (74 to 82)	70 (66 to 74)	7 (3 to 12)	.004	.96
SF-36 PCS[g]	37 (9)	42 (40 to 44)	42 (40 to 44)	0 (−3 to 3)	.85	44 (42 to 46)	40 (38 to 42)	4 (1 to 7)	.02	.53
NYHA heart failure class	2.4 (0.5)	1.7 (1.5 to 1.9)	2.1 (1.9 to 2.3)	−0.4 (−0.6 to −0.2)	<.001	1.8 (1.6 to 2.0)	2.1 (1.9 to 2.3)	−0.4 (−0.5 to −0.2)	<.001	.009

Abbreviations: KCCQ, Kansas City Cardiomyopathy Questionnaire; MET, metabolic equivalent; MLHF, Minnesota Living With Heart Failure; NYHA, New York Heart Association; RER, respiratory exchange ratio; VAT, ventilatory anaerobic threshold; VE, ventilatory equivalents; $\dot{V}CO_2$, carbon dioxide production; $\dot{V}O_2$, oxygen consumption; SF-36 PCS, Short Form 36 Health Survey physical component score.

Conversion factor: 1 foot is equal to 3 meters.

[a] At follow-up visit.

[b] *P* value represents comparison of least square means at final visit following adjustment for overall baseline values, sex, and β-blocker use.

[c] MLHF Questionnaire score range is 0 through 105; higher scores indicate worse heart failure–related quality of life.

[d] $\dot{V}O_2$ per kg of lean body mass and per kg of leg lean was measured by dual energy x-ray absorptiometry; cm^2 muscle is the area of thigh muscle measured by magnetic resonance imaging.

[e] Leg muscle quality is leg power divided by thigh muscle area.

[f] KCCQ range is 0 through 100; higher scores indicate better quality of life.

[g] SF-36 PCS range is 0 through 100; the average is 50, higher scores indicate better quality of life.

Table 3. Body Composition, Cardiac Function, and Vascular Function by Factorial Group

Variable	Overall Baseline, Mean (SD)	Exercise Factorial Groups				Diet Factorial Groups				*P* Value for Interaction Between Exercise and Diet
		Least Squares Mean (95% CI)[a]		Exercise Main Effect, Difference (95% CI)	*P* Value[b]	Least Squares Mean (95% CI)[a]		Diet Main Effect, Difference (95% CI)	*P* Value[b]	
		Exercise (n = 46)	No Exercise (n = 46)			Diet (n = 46)	No Diet (n = 46)			
Body Composition										
Weight, kg	106 (18)	99 (97 to 101)	102 (100 to 104)	−3 (−5 to −1)	<.001	97 (95 to 99)	104 (102 to 106)	−7 (−9 to −5)	<.001	.82
DXA total measurements										
Nonbone lean, kg	53 (9)	51 (50 to 52)	52 (51 to 53)	−1 (−1 to 0)	.25	50 (49 to 51)	52 (51 to 53)	−2 (−3 to −1)	<.001	.24
Fat, kg	47 (10)	42 (41 to 43)	44 (43 to 45)	−2 (−3 to −1)	.001	41 (40 to 42)	46 (45 to 47)	−5 (−6 to −4)	<.001	.67
Nonbone lean, %	52 (6)	54 (53 to 55)	53 (53 to 53)	1 (0 to 1)	.07	54 (53 to 55)	52 (51 to 53)	2 (1 to 3)	<.001	.23
Fat, %	45 (6)	44 (43 to 45)	45 (44 to 46)	−1 (−1 to 0)	.06	43 (42 to 44)	46 (45 to 47)	−2 (−3 to −1)	<.001	.24
MRI measurements										
Thigh										
Subcutaneous fat, cm^2	165 (78)	149 (145 to 153)	152 (148 to 156)	−3 (−9 to 3)	.26	143 (139 to 147)	159 (155 to 163)	−16 (−22 to −10)	<.001	.13
SM, cm^2	122 (26)	117 (115 to 119)	118 (116 to 120)	−2 (−4 to 1)	.26	115 (113 to 117)	120 (118 to 122)	−6 (−9 to −3)	<.001	.91
IMF, cm^2	25 (9)	24 (22 to 26)	25 (23 to 27)	−1 (−2 to 0)	.19	24 (22 to 26)	25 (23 to 27)	−1 (−2 to 1)	.31	.40
SM:IMF ratio	5.4 (2.4)	5.6 (5.4 to 5.8)	5.5 (5.3 to 5.7)	0.1 (−0.3 to 0.5)	.55	5.6 (5.4 to 5.8)	5.5 (5.3 to 5.7)	0.1 (−0.3 to 0.5)	.53	.25
Abdominal										
Subcutaneous fat, cm^2	378 (152)	341 (329 to 353)	346 (336 to 356)	−5 (−20 to 11)	.55	321 (311 to 331)	372 (360 to 384)	−51 (−66 to −35)	<.001	.86
Visceral fat, cm^2	213 (108)	188 (180 to 196)	198 (190 to 206)	−10 (−22 to 2)	.11	180 (172 to 188)	211 (203 to 219)	−31 (−43 to −19)	<.001	.88
Epicardial fat, cm^3	36 (17)	38 (36 to 40)	36 (34 to 38)	2 (−2 to 6)	.33	37 (35 to 39)	36 (32 to 40)	1 (−3 to 5)	.66	.54
Pericardial fat, cm^3	64 (41)	55 (51 to 59)	58 (54 to 62)	−3 (−9 to 2)	.24	55 (51 to 59)	58 (54 to 62)	−3 (−9 to 3)	.31	.23
Cardiac Function										
MRI measurements										
Mass, g	95 (19)	94 (92 to 96)	92 (90 to 94)	3 (−1 to 6)	.10	91 (89 to 93)	95 (93 to 97)	−4 (−7 to 0)	.03	.10
End diastolic volume, mL	122 (25)	122 (118 to 126)	124 (120 to 128)	−1 (−8 to 6)	.84	124 (120 to 128)	122 (116 to 128)	2 (−5 to 9)	.64	.05
Ejection fraction, %	61 (6)	61 (59 to 63)	61 (59 to 63)	0 (−2 to 2)	.89	61 (59 to 63)	62 (60 to 64)	−1 (−3 to 1)	.53	.04
Echo-Doppler measurements										
Left ventricular mass, g	212 (59)	213 (205 to 221)	208 (200 to 216)	5 (−6 to 16)	.36	211 (203 to 219)	210 (202 to 218)	0 (−10 to 11)	.93	.71
Relative wall thickness[c]	0.57 (0.11)	0.55 (0.53 to 0.57)	0.56 (0.54 to 0.58)	−0.01 (−0.03 to 0.01)	.25	0.54 (0.52 to 0.56)	0.57 (0.55 to 0.59)	−0.03 (−0.05 to −0.01)	.005	.75
Left atrium diameter, cm	4.0 (0.5)	4.0 (4.0 to 4.0)	4.0 (4.0 to 4.0)	0 (−0.1 to 0.1)	.75	4.0 (4.0 to 4.0)	4.0 (4.0 to 4.0)	0 (0 to 0.1)	.42	.84
Cardiac index, $L/min/m^2$[d]	4.6 (1.1)	4.7 (4.5 4.9)	4.8 (4.6 to 5.0)	−0.02 (−0.41 to 0.36)	.90	4.8 (4.6 to 5.0)	4.7 (4.5 to 4.9)	0.05 (−0.33 to 0.43)	.78	.42
E/A ratio	0.87 (0.20)	0.88 (0.82 to 0.94)	0.89 (0.83 to 0.95)	−0.02 (−0.09 to 0.06)	.73	0.93 (0.87 to 0.99)	0.83 (0.77 to 0.89)	0.10 (0.02 to 0.17)	.01	.13
E', cm/s	6.2 (1.5)	6.1 (5.7 to 6.5)	6.3 (5.9 to 6.7)	−0.2 (−0.7 to 0.4)	.56	6.2 (5.8 to 6.6)	6.2 (5.8 to 6.6)	0.1 (−0.5 to 0.6)	.82	.76
E/e' ratio	13.0 (3.6)	13.1 (12.1 to 14.1)	12.9 (11.9 to 13.9)	0.1 (−1.3 to 1.6)	.80	13.3 (12.3 to 14.3)	12.7 (11.7 to 13.7)	0.6 (−0.8 to 2.0)	.39	.28
Vascular function										
Arterial stiffness, cm/s[e]	1047 (291)	994 (925 to 1063)	1009 (938 to 1080)	−15 (−115 to 85)	.77	977 (906 to 1048)	1026 (957 to 1095)	−50 (−150 to 51)	.34	.77

Abbreviations: DXA, dual x-ray absorptiometry; E, E-wave velocity; E/A, early to atrial filling velocity; e', early mitral annulus velocity (septal); IMF, intermuscular fat; MRI, magnetic resonance imaging; SM, skeletal muscle.

[a] At follow-up visit.

[b] *P* value represents comparison of least square means at final visit following adjustment for overall baseline values, sex, and β-blocker use.

[c] Relative wall thickness is the ratio of wall thickness divided by chamber size.

[d] Cardiac output measured by Doppler echocardiography left ventricular outflow tract technique.

[e] Arterial stiffness determined using pulse wave velocity from carotid to femoral artery by Doppler echocardiography.

Inflammation and Lipids

With diet but not exercise, high-sensitivity C-reactive protein was significantly reduced (main effect: diet, −2.8 µg/L [95% CI, −4.9 to −0.7], P = .02; exercise, −0.4 [95% CI, −2.5 to 1.6], P = .44); changes in plasma interleukin-6 were nonsignificant (main effect: diet, −0.8 pg/mL [95% CI, −1.5 to −0.1], P = .09; exercise, 0.4 mL [95% CI, −0.3 to 1.1], P = .51); and there was no interaction (eTable 4 in the Supplement). The reduction in high-sensitivity C-reactive protein correlated with the reduction in weight (r = 0.29; P = .005). With diet but not exercise, there were significant reductions in total cholesterol (to convert cholesterol to mmol/L, multiply by 0.0259; main effect: diet, −14 mg/dL [95% CI, −24 to −14], P = .008; exercise, −4 mg/dL [95% CI, −14 to 6], P = .40) and low-density lipoprotein cholesterol (to convert low-density lipoprotein cholesterol to mmol/L, multiply by 0.0259; main effect: diet, −13 mg/dL [95% CI, −21 to −4], P = .008; exercise, −4 mg/dL [95% CI, −12 to 4], P = .35) (eTable 4 in the Supplement); these changes persisted after adjustment for lipid-lowering medications.

Associations With Change in Exercise Capacity

In the overall groups combined, change in peak $\dot{V}O_2$ was inversely related to change in total mass and fat mass, and was positively related to change in percentage of lean body mass and thigh skeletal muscle to intermuscular fat ratio (SM:IMF) (eFigure 3 in the Supplement); there were also correlations with change in left ventricular mass (r = −0.27; P = .02) and high-sensitivity C-reactive protein (r = −0.21; P = .047). Similar results were observed with exercise time as the exercise capacity variable. Multiple stepwise regression showed that sex and change in total mass were the only independent predictors of change in peak $\dot{V}O_2$ (eMethods in the Supplement).

Intervention Fidelity

Participants completing the exercise interventions attended a median of 84% (SD, 14%) of the exercise sessions, and together progressed from an average 19 minutes (SD, 6) at a 2.8 MET (SD, 0.4) at week 1 to an average 49 minutes (SD, 10) at a 3.8 MET (SD, 1.2) at week 20. Further details regarding attendance and progression are in the Supplement.

The average actual caloric intake deficit was −388 kcal/d (SD, 55) for diet-only participants and −355 kcal/d (SD, 23) for exercise + diet participants. Dietary adherence (actual vs prescribed calorie level) from recorded food logs was 99% (SD, 1%) for both diet groups.

Adverse Events

Five adverse events judged as possibly related to the intervention occurred among 5 participants: hypoglycemia between meals in 2 participants (diet and exercise + diet groups), ankle pain and swelling later diagnosed as partial tendon tear (exercise + diet group), stress foot fracture (exercise group), and an episode of unusual shortness of breath during exercise (exercise group). Three participants had a total of 6 hospitalizations, all judged unrelated to study participation: 1 participant was hospitalized for pancreatitis (exercise group), 1 participant had 3 hospitalizations for heart failure exacerbation or dyspnea (exercise + diet group), and 1 participant had 2 hospitalizations for leg edema, pain, and erythema (control group). There were no deaths.

Discussion

The major novel findings of this randomized clinical trial are that among older obese participants with chronic, stable HFPEF, intentional weight loss via Caloric restriction diet was feasible, appeared safe, and significantly improved the co-primary outcome of exercise capacity. The combination of diet with exercise, the only intervention previously shown to improve exercise capacity in HFPEF,[15,16,25] produced a robust increase in exercise capacity (+2.5 mL/kg/min $\dot{V}O_2$, substantially greater than the accepted clinically meaningful increase of 1.0 mL/kg/min). The co-primary outcome of QOL, as measured by the MLHF total score, did not show a significant change with either exercise or diet compared with control. There was also a significant change in 2 other standardized measures of QOL, the KCCQ score (a heart failure–specific QOL instrument) and the SF-36 physical score (a general QOL instrument). These were exploratory QOL measures that raised the possibility of an effect on QOL.

These results are credible because studies of diet alone or in combination with exercise in non–heart failure clinical populations have shown similar overall findings.[11,12] In a randomized clinical trial with similar design and sample size of obese, frail, older adults, diet, exercise, and their combination significantly improved peak $\dot{V}O_2$ and other measures of physical function and the effects of diet and exercise were additive (complementary).[11] Other studies also have shown significantly greater improvements in body composition with diet than exercise.[11,26] Our finding of more improvement in exploratory QOL measures with diet than with exercise is also credible based on prior exercise and diet studies in obese older persons[11] and because exercise has not consistently improved QOL in HFPEF.[15,16,25] Furthermore, preliminary reports have indicated that weight reduction via bariatric surgery can prevent the onset of heart failure, and can improve exercise capacity in patients with heart failure and reduced ejection fraction (HFREF).[27,28]

As others have indicated, peak $\dot{V}O_2$ relative to body weight (mL/kg/min), the preplanned co-primary outcome, is the most relevant measure of exercise capacity during weight-bearing (treadmill) exercise.[11,29] A true increase in exercise tolerance with diet is further supported by (1) significant increases in 4 other measures that are relatively independent of body mass ($\dot{V}O_2$ reserve, exercise time to exhaustion, workload, 6-minute walk distance); (2) preservation of absolute peak $\dot{V}O_2$ (mL/min); and (3) improvement in leg power that occurred despite significant loss of muscle mass. The largest increase in exercise capacity was with exercise and diet combined.

What are the potential mechanisms underlying improved exercise capacity? Increased adipose tissue mass promotes inflammation, hypertension, insulin resistance, and dyslipidemia resulting in impaired cardiac, arterial, and skeletal

muscle function, all of which contribute to reduced exercise capacity in patients with HFPEF[9,30-34] and can be reversed with diet.[6,8,9,13,35] Using DXA, we recently reported that percentage of body fat and percentage of leg fat were significantly increased whereas percentage of body lean and leg lean mass were reduced in older participants with HFPEF vs controls and were related to reduced exercise capacity.[10] Using MRI, we found that older participants with HFPEF have increased thigh IMF, despite a normal amount of subcutaneous fat.[6] Furthermore, the SM:IMF ratio was increased, and both IMF area and SM:IMF ratio were independent predictors of peak $\dot{V}O_2$.[6] IMF may compete with muscle tissue for critical blood flow during exercise reducing perfusive oxygen.[36] IMF may also reduce diffusive oxygen transport by increasing the distance oxygen must traverse from the capillary to the muscle mitochondria. Furthermore, increased IMF may reduce skeletal muscle capillary density and mitochondrial biogenesis and oxidative metabolism, all of which are abnormal in HFPEF.[32,34,37] In our study, increased peak $\dot{V}O_2$ was associated with reduced fat mass, increased percentage of lean mass and thigh SM:IMF ratio, and reduced inflammation biomarkers. Thus, improvement in peak $\dot{V}O_2$ from diet and exercise may be due to reduced inflammation and enhanced mitochondrial function, attenuated reactive oxygen species generation, increased vascular oxidative stress resistance, increased nitric oxide bioavailability, and improved microvascular function. Together, these may increase diffusive oxygen transport or oxygen utilization by the active muscles.[38]

With diet, left ventricular mass and relative wall thickness decreased and left ventricular E/A ratio increased, but we observed no other improvements in resting cardiac function. We also observed no significant changes in epicardial or pericardial fat, in contrast with reduced adipose tissue elsewhere. Although we did not measure cardiac function during exercise, these data suggest that the improvements we observed with diet and its combination with exercise may be due primarily to favorable "noncardiac" peripheral adaptations, in accord with reports of exercise in HFPEF.[16,33]

Because of the reported "heart failure obesity paradox" (lower mortality observed in overweight or obese individuals),[5] before diet can be recommended for obese patients with HFPEF, further studies likely are needed to determine whether these favorable changes are associated with reduced clinical events. However, a recent meta-analysis of randomized trials among older patients without heart failure indicates that intentional weight loss from diet is associated with a 15% reduction in total mortality.[39]

As observed in other diet studies and despite adequate protein intake, there was a significant decrease in muscle mass with diet that was not prevented by exercise. Although the long-term consequences of this are unclear, the muscle loss did not prevent increases in exercise capacity or leg power. Inclusion of strength training may have reduced loss of muscle mass during diet.

Limitations

This was a randomized clinical trial with frequent monitoring, professionally administered diet, and medically supervised exercise; safety and efficacy could differ under other conditions. The minimum BMI was 30, which includes most patients with HFPEF.[4,5] However, our data do not address safety and efficacy of diet in patients with lower BMI.

Our participants had typical clinical features of HFPEF (including severe exercise intolerance, left ventricular hypertrophy, and diastolic dysfunction, 76% on maintenance diuretics) and met predetermined criteria for HFPEF utilized in prior publications and recommended by the American Heart Association and the American College of Cardiology[14] and European Society of Cardiology. The relatively modest BNP levels likely result from (1) nonhospitalized, stable participants who were clinically well-compensated as required for exhaustive exercise testing and the 20-week intervention; (2) a strong, inverse relation that exists between BNP and BMI,[40] such that, when matched for other disease variables, BNP is much lower in obese than nonobese patients with HFPEF, frequently less than 100 pg/mL[40,41]; (3) BNP levels are significantly lower in HFPEF than HFREF due to lower left ventricular wall stress.[23]

Conclusions

Among obese older patients with clinically stable HFPEF, caloric restriction or aerobic exercise training increased peak $\dot{V}O_2$, and the effects may be additive. Neither intervention had a significant effect on quality of life as measured by the MLHF Questionnaire.

ARTICLE INFORMATION

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