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Relation Between Body Mass Index, Exercise Training, and Outcomes in Chronic Systolic Heart Failure

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Abstract

Exercise training (ET) in heart failure (HF), as demonstrated in the HF-ACTION trial, was associated with improved exercise tolerance and health status, and a trend towards reduced mortality or hospitalizations. This analysis of the HF-ACTION cohort examines the effect of ET in overweight and obese compared to normal HF subjects. 2,314 of 2,331 systolic HF subjects randomized to aerobic ET vs. usual care in HF-ACTION were analyzed to determine the effect of ET on all cause mortality, hospitalizations, exercise parameters, quality of life (QOL), and body weight changes by subgroups of body mass index (BMI). Strata included normal weight (BMI 18.5 – 24.9 kg/m²), overweight (BMI 25.0 – 29.9 kg/m²), obese I (BMI 30 – 34.9 kg/m²), obese II (BMI 35–39.9 kg/m²), and obese III (BMI ≥ 40 kg/m²). At enrollment, 19.4% of subjects were normal weight, 31.3% overweight, and 49.4% obese. Higher BMI was associated with a non-significant increase in all cause mortality or hospitalization. ET was associated with non-significant reductions in all cause mortality or hospitalization in each weight category (HR 0.98, 0.95, 0.92, 0.89, and 0.86 in normal weight, overweight, obese I, obese II, and obese III categories, respectively [all p>0.05]). Modeled improvement in exercise capacity (peak oxygen consumption) and QOL in the ET group was seen in all BMI categories. In conclusion, aerobic ET in HF was

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associated with a non-significant trend towards decreased mortality and hospitalizations and a significant improvement in QOL across the range of BMI categories.

Keywords

heart failure; body mass index; exercise

Introduction

In HF patients, increased body mass index (BMI) has been associated with lower quality of life (QOL) as well as lower exercise tolerance, as measured by peak oxygen consumption (PKVO_2 , mL/kg/min).^{1,2} However, contrary to expectations, increased BMI has been associated with improved, rather than impaired, outcomes in a broad range of HF; this has been termed the “obesity paradox”.³⁻⁵ The overall results from the HF-ACTION trial demonstrated that aerobic exercise training (ET) in systolic HF patients was associated with a non-significant trend towards reduction in mortality or hospitalizations and a substantial improvement in health status.^{6,7} This paper examines whether overweight and obese HF patients in the HF-ACTION trial derive differential benefit from ET in terms of health status and clinical outcomes.

Methods

A Controlled Trial Investigating Outcomes of Exercise Training (HF-ACTION) was a multi-center, randomized trial (1:1) of ET vs. usual care in patients with left ventricular systolic dysfunction and symptomatic HF. Inclusion criteria were left ventricular ejection fraction (LVEF) $\leq 35\%$, NYHA class II-IV symptoms, stable, optimal medical therapy for 6 weeks prior to randomization, and ability to exercise.⁸ BMI (weight in kg / height² in m²) recorded at baseline was available in 2324 of 2331 subjects. Subjects were divided into categories based on BMI as defined by the International Obesity Taskforce: underweight (BMI < 18.5 kg/m²), normal weight (BMI 18.5 – 24.9 kg/m²), overweight (BMI 25.0 – 29.9 kg/m²), obese I (BMI 30 – 34.9 kg/m²), obese II (BMI 35-39.9 kg/m²), and obese III (BMI ≥ 40 kg/m²).⁹ Since only 10 subjects fell into the underweight category, those subjects were excluded from analysis, leaving a final study cohort of $n = 2314$.

HF-ACTION study subjects underwent baseline cardiopulmonary exercise testing (CPX) prior to randomization. The primary method used for exercise testing was a modified Naughton treadmill protocol. For patients unable to exercise on a treadmill, or at certain sites, cycle ergometer was used (20 watts/ 2 minute stage or 10 watts / min ramp). At most sites, respiratory gas exchange was recorded during exercise testing, in addition to blood pressure and continuous EKG recordings. All patients were strongly encouraged to exercise to a sign and symptom-limited maximal exertion.⁸ Multiple physiologic variables obtained via CPX testing were determined, including PKVO_2 , anaerobic threshold, and $\text{V}_E/\text{V}_{\text{CO}_2}$, maximum heart rate, and exercise time. PKVO_2 is defined as oxygen uptake at peak exercise, and can be described as an absolute value (mL/min) or relative to body weight (mL/kg/min). Ventilatory-derived anaerobic threshold, the VO_2 at which ventilation increases disproportionately relative to VO_2 and work, also known as the lactate threshold, was determined by the modified v-slope method by two blinded reviewers (mL/kg/min). $\text{V}_E/\text{V}_{\text{CO}_2}$, the slope of ventilation to carbon dioxide output, is the most widely studied index of ventilatory efficiency.^{10,11} Furthermore, 6-minute walk tests were performed at baseline to determine sub-maximal exercise capacity (meters). All CPX data were analyzed by a core laboratory.

Patients randomized to ET initially participated in supervised group exercise sessions 3 times a week for 3 months. The primary training mode was walking, treadmill, or stationary bicycle. The patients transitioned to home exercise with study-provided equipment after 36 group sessions, with a goal of exercising 5 times a week for 40 minutes. Patients in the usual care group were advised to exercise at moderate pace 30 minutes on most days but did not participate in the supervised training.⁶

The primary endpoint of this analysis was the primary endpoint of the HF-ACTION trial, a composite of all-cause mortality or all-cause hospitalization. The secondary endpoints analyzed were 1) all cause mortality and 2) cardiovascular death or cardiovascular hospitalization. Other endpoints assessed in this analysis were changes in six-minute walk distance (6MWD, meters), PKVO₂, duration of exercise (minutes) on CPX, QOL, as assessed by Kansas City Cardiomyopathy Questionnaire (KCCQ), and weight (kg).

Baseline demographic data, clinical data, and CPX data were analyzed by BMI category. Data are expressed as median and interquartile range or percentage of total. The relationship between continuous variables and continuous BMI was assessed by linear regression and the relationship between categorical variables and BMI was assessed by logistic regression. Kaplan Meier Survival plots were analyzed by BMI category. Cox proportional hazards models were used to estimate the relationship between BMI and the primary and secondary endpoints of the trial. The model for the primary endpoint tested for interactions between BMI and treatment group. A multivariable Cox model including over 50 candidate predictor variables was constructed for the primary endpoint. The final set of predictors of the primary endpoint was objectively selected using a stepwise variable selection based on a bootstrap-backward selection process. Multiple imputation was used to replace missing data for covariates. It was found that there was a relationship between baseline BMI and missing data in CPX, QOL, and weight variables. Since it was likely that the data were not missing at random, a mixed model approach was also used for comparison of the change in CPX, QOL, and weight variables to the BMI and treatment groups. Statistical analyses were performed using SAS. All statistical tests were 2-tailed with statistical significance defined to be at the 0.05 level.

Results

The baseline characteristics and baseline exercise variables of the study cohort stratified by BMI category are described in Table 1. Increased BMI was associated with higher absolute PKVO₂ (mL/min) but lower relative PKVO₂ (mL/kg/min). V_E/V_{CO2} slope, CPX exercise time, and 6MWD all decreased with increasing BMI category.

In this study cohort, 1539 subjects had a primary endpoint event. Continuous BMI was not a significant predictor of the primary outcome of all cause mortality or hospitalization (relative risk [RR] 1.004, 95% confidence interval [CI] 0.997 – 1.011, P=0.24). Even after adjustment for treatment category (ET vs. usual care) and additional explanatory variables, continuous baseline BMI was not associated with the primary endpoint (BMI P=0.45, ET P=0.80, interaction P=0.91). Kaplan Meier survival plots for the BMI categories are shown in Figure 1.

The effects of ET on the primary and secondary endpoints after stratification by BMI category are shown in Table 2. ET was associated with a non-significant trend toward reduction in events in the overall cohort and in each BMI category for all endpoints. Although, for each endpoint, the hazard ratios associated with treatment tend to decrease with increasing BMI category, the relationship was not statistically significant.

Change in exercise variables, QOL, and weight over time were also assessed by BMI category (Table 3). As there was a relationship between the baseline BMI and the rates of missing CPX, KCCQ, and weight data, these results should be interpreted with caution. There was a significant difference by BMI and treatment for the change in PKVO₂, CPX duration, QOL by KCCQ, and weight (all $p < 0.05$), but not 6MWD ($p = 0.12$). Change in PKVO₂ (mL/min) at 3 months and weight loss at 3 months were significantly correlated ($r = 0.17$, $p\text{-value} = 0.0005$); for every kg increase in 3-month weight change, it was estimated that PKVO₂ increased by 17.6 mL/min. However, as baseline BMI increased, the association between weight changes and PKVO₂ lessened ($p = 0.045$); for each unit increase in BMI, the increase in PKVO₂ (mL/min) associated with weight loss was decreased by 0.3 mL/min.

Discussion

Both overweight and obesity are common in HF, and devising optimal recommendations and treatment strategies for this cohort of patients is important. Among subjects with chronic HF enrolled in HF-ACTION, nearly 50% of patients were classified as obese. The overall HF-ACTION trial demonstrated a non-significant trend towards reduced events in HF patients randomized to ET.⁶ The current study shows that the effect of ET is similar across the categories of BMI; exercise was neither more helpful nor more dangerous in overweight or obese patients with HF. Modest improvements in health status and weight loss with exercise training were observed in HF patients with elevated BMI compared to those with normal BMI. These findings suggest that ET is safe, and may modestly benefit overweight and obese HF patients in terms of weight loss and QOL, resulting in improved self-efficacy. The weight changes achieved in this study with ET, however, were very modest; the effects of ET on perceptions of health are more likely to be a result of participation in the structured exercise program itself.

In the overall HF-ACTION cohort, a modest but statistically significant improvement in self-reported health status was seen in the exercise group compared to usual care group.⁷ QOL at baseline, as quantified by the KCCQ, was lower in the obese categories, with a slightly greater degree of improvement in QOL with exercise seen in the obese subjects.

We have previously found in this cohort that although elevated BMI is associated with higher absolute PKVO₂ (mL/min), elevated BMI is a strong, independent predictor of low relative PKVO₂ (mL/kg/min).⁵ Higher BMI is also associated with lower O₂ pulse, anaerobic threshold, and V_E/V_{CO_2} . On multivariable analysis, BMI was a significant, independent predictor of lower PKVO₂, with a slightly weaker relationship between BMI and V_E/V_{CO_2} slope.² In this analysis, PKVO₂ in the ET group tended to increase over time more than for the patients in the usual care group ($P = 0.0059$). However, the improvement in exercise tolerance as assessed by absolute PKVO₂ (mL/min) and relative PKVO₂ (mL/kg/min) was also seen over the range of BMI categories.

In this cohort, BMI was not predictive of the primary outcome of all cause mortality or all cause hospitalization. Previous reports have found high BMI to be associated with lower mortality in HF, and this has been termed an “obesity paradox”.¹² One possible explanation for this discrepancy is that the exclusion of patients not able to exercise might have created a cohort of patients in which BMI is less predictive of outcome. BMI has not previously been demonstrated to predict HF hospitalizations.⁴

Our study has all the limitations of post hoc analyses from prospective randomized trials. The cross-sectional data reported above, particularly correlations among baseline variables, may be influenced by the set of patients who chose to enroll in this clinical trial. BMI was

our only index of obesity; there are no measures of body composition or fat mass or other anthropometric indices such as waist circumference or waist-to-hip ratio. In a recent study, WHO classification by BMI when compared to the gold standard of DEXA scans misclassified HF patients 41% of the time.¹³ Underweight subjects, who may have cardiac cachexia and made up a very small percentage of the HF-ACTION study, were not analyzed. Lung volumes and measures of bronchoreactivity which may affect CPX variables were not available. We did not assess for the presences of obstructive sleep apnea which is known to independently impact baseline CPX variables in the obese.¹⁴ Furthermore, there was a relationship between the baseline BMI and the rates of missing CPX, KCCQ, and weight data; thus, the results with respect to these data must be interpreted with caution.

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Figure 1.

Kaplan Meier Plots for Primary Endpoint by Body Mass Index Category (Unadjusted).

Normal weight = BMI 18.5 – 24.9 kg/m²; overweight = BMI 25.0 – 29.9 kg/m²; obese I = BMI 30 – 34.9 kg/m²; obese II = BMI 35-39.9 kg/m²; obese III = BMI ≥ 40 kg/m².

Table 1
Baseline characteristics of the study cohort stratified by body mass index category

Variable	Body Mass Index (kg/m ²)					P value [†]
	18.5 – 24.9 (N = 448)	25.0 – 29.9 (N = 724)	30.0 – 34.9 (N = 551)	35.0 – 39.9 (N = 330)	≥ 40 (N = 261)	
Number randomized to exercise training	N=226	N=350	N=289	N=158	N=129	-
Age (years)	64 (55, 74)	63 (54, 70)	59 (51, 67)	56 (49, 62)	50 (40, 57)	<0.0001
Female Sex	32%	22%	27%	32%	37%	0.003
Race						<0.0001
Black	29%	25%	31%	40%	57%	
White	65%	69%	65%	55%	39%	
Other	6%	6%	4%	5%	4%	
Hispanic	4%	3%	4%	4%	4%	0.89
Ischemic Etiology	52%	60%	57%	44%	25%	<0.0001
Prior Myocardial Infarction	44%	50%	45%	35%	20%	<0.0001
Hypertension (history)	50%	56%	65%	67%	71%	<0.0001
Diabetes Mellitus	19%	28%	37%	39%	49%	<0.0001
Smoking Status						0.0084
Never	39%	33%	36%	38%	50%	
Current	21%	18%	15%	13%	15%	
Past	40%	50%	49%	49%	36%	
NYHA II/III-IV	63%/37%	70%/30%	63%/37%	62%/38%	51%/49%	<0.0001
Left ventricular ejection fraction (%)	24 (20, 30)	25 (20, 30)	25 (21, 30)	25 (20, 30)	25 (20, 30)	0.68
Atrial fibrillation or atrial flutter	21%	23%	21%	21%	15%	0.013
Systolic blood pressure, (mmHg)	110 (98, 120)	110 (100, 128)	112 (100, 128)	112 (102, 122)	116 (104, 130)	<0.0001
Diastolic blood pressure (mmHg)	68 (60, 73)	70 (60, 78)	70 (61, 80)	70 (64, 80)	74 (66, 82)	<0.0001
Heart rate at rest, (bpm)	69 (61, 77)	69 (61, 76)	71 (63, 79)	72 (64, 80)	75 (67, 84)	<0.0001
Sodium (mmol/L)	139 (137, 141)	139 (137, 141)	139 (137, 141)	139 (137, 141)	139 (137, 141)	0.092
Creatinine (mg/dL)	1.2 (1.0, 1.5)	1.2 (1.0, 1.5)	1.2 (1.0, 1.5)	1.2 (1.0, 1.4)	1.1 (0.9, 1.3)	0.005
Blood urea nitrogen, (mg/dL)	21 (16, 29)	21 (16, 28)	21 (16, 28)	19 (14, 27)	19 (14, 26)	0.0007
Angiotensin Converting Enzyme Inhibitor or Angiotensin II Receptor Blocker	93%	94%	94%	96%	94%	0.14
Beta-blocker	94%	93%	96%	97%	96%	0.09

Variable	Body Mass Index (kg/m ²)					P value [†]
	18.5 – 24.9 (N = 448)	25.0 – 29.9 (N = 724)	30.0 – 34.9 (N = 551)	35.0 – 39.9 (N = 330)	≥ 40 (N = 261)	
Aldosterone antagonist	42%	43%	42%	49%	56%	< 0.0001
Loop diuretic	74%	73%	80%	84%	87%	< 0.0001
Digoxin	47%	44%	44%	47%	43%	0.52
Implantable Cardioverter Defibrillator	41%	43%	41%	40%	30%	0.0007
Cardiac Resynchronization Therapy	18%	20%	19%	17%	13%	0.031
Beck Depression Inventory II	7 (4, 13)	8 (4, 13)	8 (5, 15)	10 (5, 17)	10 (6, 17)	< 0.0001
Kansas City Cardiomyopathy Questionnaire/Overall Summary Score	72 (55, 88)	72 (55, 86)	66 (50, 82)	61 (47, 80)	60 (43, 76)	< 0.0001
Cardiopulmonary Exercise Testing (CPX) variables						
Peak oxygen consumption (mL/kg/min)	14.4 (11.6, 18.0)	15.1 (12.4, 18.4)	15.0 (11.2, 17.8)	13.9 (11.3, 16.6)	12.4 (10.1, 15.9)	< 0.0001
Peak oxygen consumption (mL/min)	954 (773, 1208)	1271 (985, 1565)	1430 (1077, 1760)	1520 (1231, 1865)	1661 (1277, 2115)	< 0.0001
V _E /VCO ₂ ratio	36 (30, 43)	33 (29, 39)	32 (29, 37)	30 (27, 35)	29 (25, 34)	< 0.0001
Exercise duration on CPX (min)	9.4 (6.7, 12.0)	10.3 (7.9, 13.0)	9.8 (7.1, 12.0)	9.1 (6.7, 11.6)	8.0 (5.7, 10.3)	< 0.0001
6 minute walk distance (m)	366 (296, 430)	387 (317, 446)	372 (297, 443)	362 (294, 426)	335 (274, 407)	< 0.0001
Respiratory Exchange Ratio > 1.1	47%	48%	43%	37%	32%	< 0.0001
Heart rate at peak exercise (bpm)	115 (98, 131)	119 (105, 132)	120 (103, 133)	122 (108, 136)	123 (111, 141)	< 0.0001

[†] P value by linear regression for all of the continuous variables correlated with BMI as a continuous variable. P value by logistic regression for all of the categorical variables correlated with BMI as a continuous variable

Table 2

Primary and secondary endpoint event rates and hazard ratios of exercise treatment by body mass index group with usual care as reference

Primary Endpoint		Body Mass Index (kg/m ²)				
		18.5 – 24.9	25.0 – 29.9	30.0 – 34.9	35.0 – 39.9	≥ 40
Mortality	Exercise Event Rate *	42%	40%	39%	43%	46%
	Usual Care Event rate	44%	35%	44%	46%	50%
	Treatment Hazard Ratio (95% confidence interval)	0.98 (0.83, 1.16)	0.95 (0.85, 1.06)	0.92 (0.83, 1.02)	0.89 (0.78, 1.02)	0.86 (0.71, 1.04)
	Exercise Event Rate	7%	3%	4%	3%	4%
Cardiovascular Death or Hospitalization	Usual Care Event rate	7%	5%	6%	6%	5%
	Treatment Hazard Ratio (95% confidence interval)	0.97 (0.70, 1.35)	0.95 (0.77, 1.19)	0.94 (0.76, 1.16)	0.93 (0.69, 1.24)	0.91 (0.60, 1.39)
	Exercise Event Rate	32%	33%	28%	32%	37%
	Usual Care Event rate	34%	27%	35%	39%	36%
	Treatment Hazard Ratio (95% confidence interval)	0.94 (0.78, 1.13)	0.92 (0.82, 1.04)	0.91 (0.81, 1.02)	0.90 (0.77, 1.04)	0.88 (0.72, 1.08)

† All hazard ratios were estimated using Cox Regression analysis, with BMI estimated at the mid-BMI for each category.

* All event rates are one year Kaplan-Meier rates, stratified by treatment group and body mass index (BMI) category.

Table 3
Change in exercise and health status variables according to body mass index group and treatment assignment

		Body Mass Index (kg/m ²)				
		18.5 – 24.9	25.0 – 29.9	30.0 – 34.9	35.0 – 39.9	≥ 40
Distance in 6 minute walk (meters)	Exercise Baseline to 3 months median (Q1, Q3) N	23 (-19, 61) 182	24 (-9, 61) 294	17 (-17, 50) 254	24 (-9, 63) 127	10 (-30, 55) 97
	Usual Care Baseline to 3 months median (Q1, Q3) N	9 (-29, 46) 172	4 (-27, 35) 287	7 (-29, 38) 198	4 (-27, 37) 123	4 (-31, 35) 88
Peak oxygen consumption, (mL/kg/min)	Exercise Baseline to 3 months median (Q1, Q3) N	0.4 (-0.7, 2.2) 185	0.8 (-0.7, 2.3) 304	0.6 (-1.1, 2.4) 248	0.9 (-0.4, 2.7) 130	0.3 (-0.7, 1.8) 99
	Usual Care Baseline to 3 months median (Q1, Q3) N	0.0 (-1.3, 1.2) 171	0.2 (-1.2, 1.4) 288	0.3 (-0.9, 1.5) 213	-0.2 (-1.4, 1.0) 129	0.6 (-0.7, 1.8) 91
Peak oxygen consumption, (mL/min)	Exercise Baseline to 3 months median (Q1, Q3) N	35 (-33, 149) 185	52 (-54, 184) 304	46 (-112, 206) 248	88 (-62, 263) 130	30 (-101, 228) 99
	Usual Care Baseline to 3 months median (Q1, Q3) N	13 (-79, 90) 171	20 (-100, 131) 288	20 (-100, 162) 212	-16 (-155, 112) 129	50 (-81, 215) 91
Cardiopulmonary exercise test duration (min)	Exercise Baseline to 3 months median (Q1, Q3) N	1.7 (0.2, 3.0) 193	1.5 (0.1, 3.0) 311	1.6 (0.3, 2.9) 251	1.5 (0.5, 2.9) 134	1.4 (0.3, 2.5) 102
	Usual Care Baseline to 3 months median (Q1, Q3) N	0.2 (-0.5, 1.2) 181	0.5 (-0.6, 1.5) 296	0.2 (-0.9, 1.3) 212	0.0 (-0.9, 1.1) 130	0.5 (-0.3, 1.9) 92
KCCQ Overall Summary Score	Exercise Baseline to 3 months median (Q1, Q3) N	4.7 (-2.9, 13.4) 207	4.2 (-3.5, 12.7) 320	4.7 (-2.3, 12.2) 264	6.0 (-2.1, 16.4) 143	5.7 (0.0, 18.0) 111
	Usual Care Baseline to 3 months median (Q1, Q3) N	3.1 (-3.7, 9.4) 195	2.1 (-4.2, 9.1) 318	2.6 (-6.5, 9.4) 219	2.1 (-5.5, 12.0) 139	4.5 (-4.8, 10.8) 108
Weight (kg)	Exercise Baseline to 3 months median (Q1, Q3) N	0.1 (-1.0, 1.9) 188	0.0 (-1.6, 1.1) 304	-0.5 (-2.2, 1.2) 248	-0.5 (-2.8, 1.5) 130	-0.3 (-3.7, 2.1) 101
	Usual Care Baseline to 3 months median (Q1, Q3) N	0.1 (-1.6, 1.4) 173	0.2 (-1.1, 1.6) 291	-0.1 (-2.7, 2.1) 213	0.3 (-1.4, 2.9) 130	-0.4 (-2.4, 1.6) 92

Q1 = quartile 1; Q3 = quartile 3. KCCQ = Kansas City Cardiomyopathy Questionnaire