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The Relationship Between Body Mass Index and Cardiopulmonary Exercise Testing in Chronic Systolic Heart Failure

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Abstract

Background—Cardiopulmonary exercise testing (CPX) in patients with systolic heart failure (HF) is important for determining HF prognosis and helping guide timing of heart transplantation. Although approximately 20–30% of patients with HF are obese (body mass index [BMI]>30kg/m^2), the impact of BMI on CPX results is not well established. The objective of the present study was to assess the relationship between BMI and CPX variables, including peak oxygen uptake, VO_2 at ventilatory threshold, O_2 pulse, and ventilation / carbon dioxide production ratio.

Methods—Consecutive systolic HF patients (n=2324) enrolled in the Heart Failure and A Controlled Trial Investigating Outcomes of Exercise Training (HF-ACTION) trial who had baseline BMI recorded were included in the present study. Subjects were divided into strata based on BMI: underweight (BMI< 18.5 kg/m^2), normal weight (BMI 18.5 – 24.9 kg/m^2), overweight (BMI 25.0 – 29.9 kg/m^2), obese I (BMI 30 – 34.9 kg/m^2), obese II (BMI 35–39.9 kg/m^2), and obese III (BMI ≥ 40 kg/m^2).

Results—Obese III, but not overweight, obese I, or obese II, was associated with decreased peak oxygen uptake (mL/kg/min) compared to normal weight status. Increasing BMI category was inversely related to ventilation / carbon dioxide production (VE/VCO2) ratio (p< 0.0001). On multivariable analysis, BMI was a significant independent predictor of peak oxygen uptake (partial R^2 = 0.07, p< 0.0001) and V_E/V_{CO2} slope (partial R^2 = 0.03, p< 0.0001) in patients with chronic systolic HF.

Conclusions—BMI is significantly associated with key CPX fitness variables in HF patients. The influence of BMI on the prognostic value of CPX in HF requires further evaluation in longitudinal studies.

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Introduction

Heart failure (HF) is a prevalent and highly morbid condition, with over 5 million cases in the United States.[1] In patients with advanced systolic HF, cardiopulmonary exercise testing (CPX) plays an important role in determining prognosis and optimal timing of heart transplantation.[2,3] Important prognostic CPX variables include peak oxygen uptake ($PKVO_2$), anaerobic threshold (VO_2 at ventilatory threshold [VT]), O_2 pulse, and ventilation / carbon dioxide production ratio (V_E/V_{CO2}). $PKVO_2$ is often used in decision making about listing for heart transplantation; a $PKVO_2$ of 14 mL/kg per minute is often cited as a cut-off point below which risk of mortality is high enough to warrant consideration for heart transplantation and above which heart transplantation can be safely deferred.[3–5] However, the prognostic utility of CPX and $PKVO_2$ has been questioned in special populations, including women, patients on beta-blockers, and those with obesity.[6–9]

Obesity (body mass index [BMI] $\geq$30 kg/m^2) is present in approximately 20–30% of patients with advanced HF. Furthermore, obesity, as indexed by elevated BMI, has been associated with improved, rather than impaired, outcomes in a broad range of HF patients.[10–12] Despite the improved HF prognosis observed with obesity, recent studies suggest that HF patients with obesity, as indexed by high BMI, have lower $PKVO_2$ (mL/kg/min) on CPX compared to normal weight subjects.[9,10] Since body fat mass, unlike muscle mass, is "metabolically inert", some have suggested that reporting $PKVO_2$ in mL/kg/min rather than mL/min may lead to misleadingly low values for obese subjects.[4,5,13] Given the high prevalence of obesity in HF, it is important to know how BMI may affect CPX variables used in determining HF prognosis. Thus, the objective of this study is to further investigate the impact of BMI on CPX results, including $PKVO_2$, VO_2 at VT, O_2 pulse, and V_E/V_{CO2}.

Methods

Heart Failure and A Controlled Trial Investigating Outcomes of Exercise Training (HF-ACTION) was a multi-center, randomized trial (1:1) of exercise training vs. usual care in patients with left ventricular systolic dysfunction and symptomatic HF. Major 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, as described previously.[14] Subjects with baseline BMI (n=2324) recorded were included in the present analysis.

There were 2329 of 2331 HF-ACTION study subjects who underwent baseline CPX testing 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 those testing sites that routinely used this modality for exercise testing, a leg ergometer was used (20 watts/ 2 minute stage or 10 watts / min ramp). Respiratory gas exchange was recorded during exercise testing, in addition to blood pressure and continuous EKG recordings. Patients were strongly encouraged to exercise to a sign and symptom-limited maximal exertion.[14] Multiple physiologic variables obtained via CPX testing were determined, including $PKVO_2$, VO_2 at VT, O_2 pulse, and V_E/V_{CO2}, 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 (VO_2 at VT), 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). O_2 pulse is defined as $PKVO_2$ in mL/min divided by peak heart rate and is expressed as mL/kg/beat. V_E/V_{CO2} is the slope of ventilation to carbon dioxide output [5]. 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.

BMI (weight in kg / height in m^2), which strongly correlates with body fat mass, was recorded at baseline in all subjects included in the present analysis. Subjects were divided into groups based on BMI as defined by the International Obesity Taskforce: underweight (BMI< 18.5 kg/m^2), normal weight (BMI 18.5 – 24.9 kg/m^2), overweight (BMI 25.0 – 29.9 kg/m^2), obese I (BMI 30 – 34.9 kg/m^2), obese II (BMI 35–39.9 kg/m^2), and obese III (BMI ≥ 40 kg/m^2).[15] Baseline demographic data, clinical data, and CPX data were analyzed by BMI category. Data are expressed as median and interquartile range. The correlation between continuous variables and BMI was assessed by Pearson's r correlation coefficient. Separate multivariable linear regression models were fit for PKVO2 and V_E/V_{CO2}, respectively. For each multivariable model, a list of 33 candidate predictor variables was considered for inclusion in the multivariable model. Those variables are listed in Table 4. From the 33 variables, those with the highest p-values were sequentially eliminated according to the partial F-test from inclusion in the multivariable model until all remaining variables had multivariable $p<0.05$. From the remaining variables, those variables with partial R-square <0.01 were eliminated from inclusion in the final multivariable model. The variables which were included in the final multivariable model all have partial R-square ≥ 0.01.

Statistical analyses were performed using SAS version 9.0 (SAS Institute, Inc, Cary, North Carolina) and R version 2.7.1 (R Foundation for Statistical Computing, Vienna, Austria). All statistical tests were 2-tailed with statistical significance defined to be at the 0.05 level.

Results

Of 2331 subjects randomized, 2324 had complete baseline BMI data and were included in the present analysis. Median LVEF in the study cohort was 25% (25^{th}–75^{th} percentiles: 20% – 30%). The NYHA II, III, and IV class representation were 63%, 36%, and <1%, respectively; 94% of the patients were on an angiotensin converting enzyme inhibitor or angiotensin receptor blocker, 94% were on a beta-blocker, and 18% had biventricular pacemakers. The baseline characteristics of the cohort stratified by BMI category are displayed in Table 1. Higher BMI category was associated with younger age and higher likelihood of black race ($p<0.0001$). Elevated BMI was associated with a lower overall score on the Kansas City Cardiomyopathy Questionnaire, suggesting a lower disease specific health status[16]

Table 2 outlines the physiologic exercise variables by BMI category. For all of the exercise variables besides VO_2 at VT, data was non-missing in over 96% of the patients. For VO_2 at VT, data was non-missing in 83% of the patients. Absolute $PKVO_2$ (mL/min) increased with increasing BMI category. However, relative $PKVO_2$ (mL/kg/min) was lowest in the Obese III category and not qualitatively different among the normal weight, overweight, and Obese I categories. Scatterplots depicting the relationship between BMI and $PKVO_2$ (ml/min) and between BMI and $PKVO_2$ (ml/kg/min) are displayed in Figures 1a and 1b, respectively. VO_2 at VT, O_2 pulse, V_E/V_{CO2} slope, and exercise time all decreased with increasing BMI category. Distance on six-minute walk test also decreased with increasing BMI category.

In multivariable linear regression analysis for prediction of $PKVO_2$ (mL/kg/min) as a continuous variable (Table 3), BMI was a strong predictor of $PKVO_2$, second only to age among the variables examined from Table 4. The other significant variables associated with $PKVO_2$ in multivariable analysis were history of diabetes, gender, geographic region, LVEF, mode of CPX, NYHA class, history of peripheral vascular disease, race, and ventricular conduction on EKG. When $PKVO_2$ was analyzed as a categorical variable on logistic regression analysis, the same variables were found to predict low $PKVO_2$ (≤ 14 mL/kg/min). BMI was also found to be a significant predictor of V_E/V_{CO2} slope (Table 5, Figure 2).

Discussion

Historically, $PKVO_2$ has been the most widely used CPX variable in determining HF prognosis and timing of transplant; however, other variables determined by CPX, including percent predicted $PKVO_2$, V_E/V_{CO2} slope, and O_2 pulse, are also prognosticators in chronic systolic HF.[3,4,17–20] CPX results are also used to evaluate functional status, guide exercise prescriptions, and assess efficacy of therapy in HF.[21] Given the prevalence of obesity in HF, the impact of BMI on physiologic variables obtained from CPX is important to determine. This is the largest study, to our knowledge, to systematically explore the relationship between BMI and results of CPX in patients with chronic HF and LVEF≤35%. We have found that although elevated BMI is associated with higher absolute $PKVO_2$ (mL/min), elevated BMI is an independent predictor of low relative $PKVO_2$ (mL/kg/min). Higher BMI is also associated with lower O_2 pulse, VO_2 at VT, and V_E/V_{CO2}. On multivariable analysis, BMI remains a significant predictor of V_E/V_{CO2} slope, although the relationship between BMI and V_E/V_{CO2} is weaker than that between BMI and $PKVO_2$.

Although obesity is associated with increased risk of new onset HF [22], a surprising relationship between BMI and outcomes in those with established HF has been observed. Counter to expectations, high BMI, or overweight/obesity, is consistently associated with better HF outcomes. This “obesity paradox” in HF has been confirmed in diverse HF populations, including advanced HF patients awaiting transplant, stable outpatients with HF enrolled in clinical trials, and hospitalized patients with acute decompensated HF.[10–12,23] Recent studies suggest that despite better prognosis with obesity, HF patients with high BMI have lower $PKVO_2$ (mL/kg/min).[9,10] Furthermore, in apparently healthy subjects and coronary artery disease patients, a graded inverse relationship between BMI and $PKVO_2$ (mL/kg/min) has been demonstrated.[24,25] The $PKVO_2$ of morbidly obese subjects without apparent heart disease has been shown to be in the same low range as that for NYHA III–IV HF patients.[25]

It has been suggested that reporting $PKVO_2$ in mL per kg of total body weight may result in misleadingly low values for obese subjects, since a large percentage of body weight may be fat mass, which does not metabolize O_2. [4,5,13] In fact, several studies of HF patients have demonstrated $PKVO_2$ adjusted for lean body mass (as determined by skin-fold thickness or DEXA scan) may be a better discriminator of prognosis in chronic HF compared to $PKVO_2$ adjusted for total body weight.[26–28] However, valid and reliable measures of body composition may not be available during routine CPX. Other studies have shown that O_2 pulse or V_E/V_{CO2} slope may be better predictors of prognosis compared to $PKVO_2$ in patients with high BMI or obesity.[20,29] Of note, lower V_E/V_{CO2}, which was associated with higher BMI in the current analysis, corresponds to better prognosis in subjects with chronic HF.

Limitations

A limitation of this study is that BMI is our only index of obesity; there are no measures of body composition or fat mass. Measures of pulmonary function which may affect CPX variables were not available. This is a cross-sectional study of baseline variables in a large randomized-controlled trial; a future report will assess the interaction between BMI and CPX variables on prognosis.

Conclusions

In this large, well-characterized cohort of HF patients undergoing CPX, BMI is a strong independent predictor of lower relative $PKVO_2$. Higher BMI is also independently associated with lower V_E/V_{CO2} slope. Longitudinal studies are needed to assess which CPX variables are the best predictors of prognosis in obese HF patients.

Acknowledgments

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HF-ACTION is registered: www.clinicaltrials.gov, study number NCT00047437

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Figure 1a:

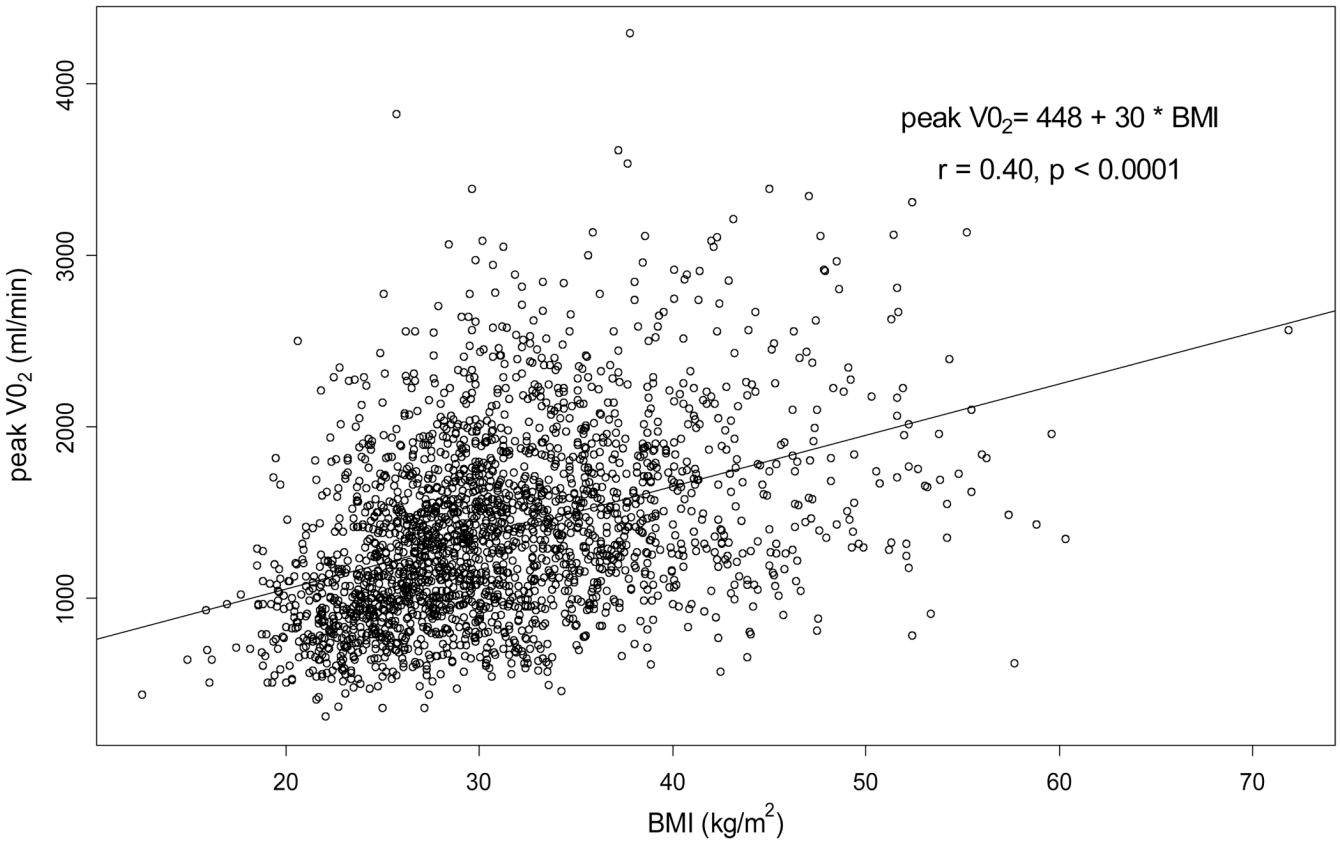

Figure 1b

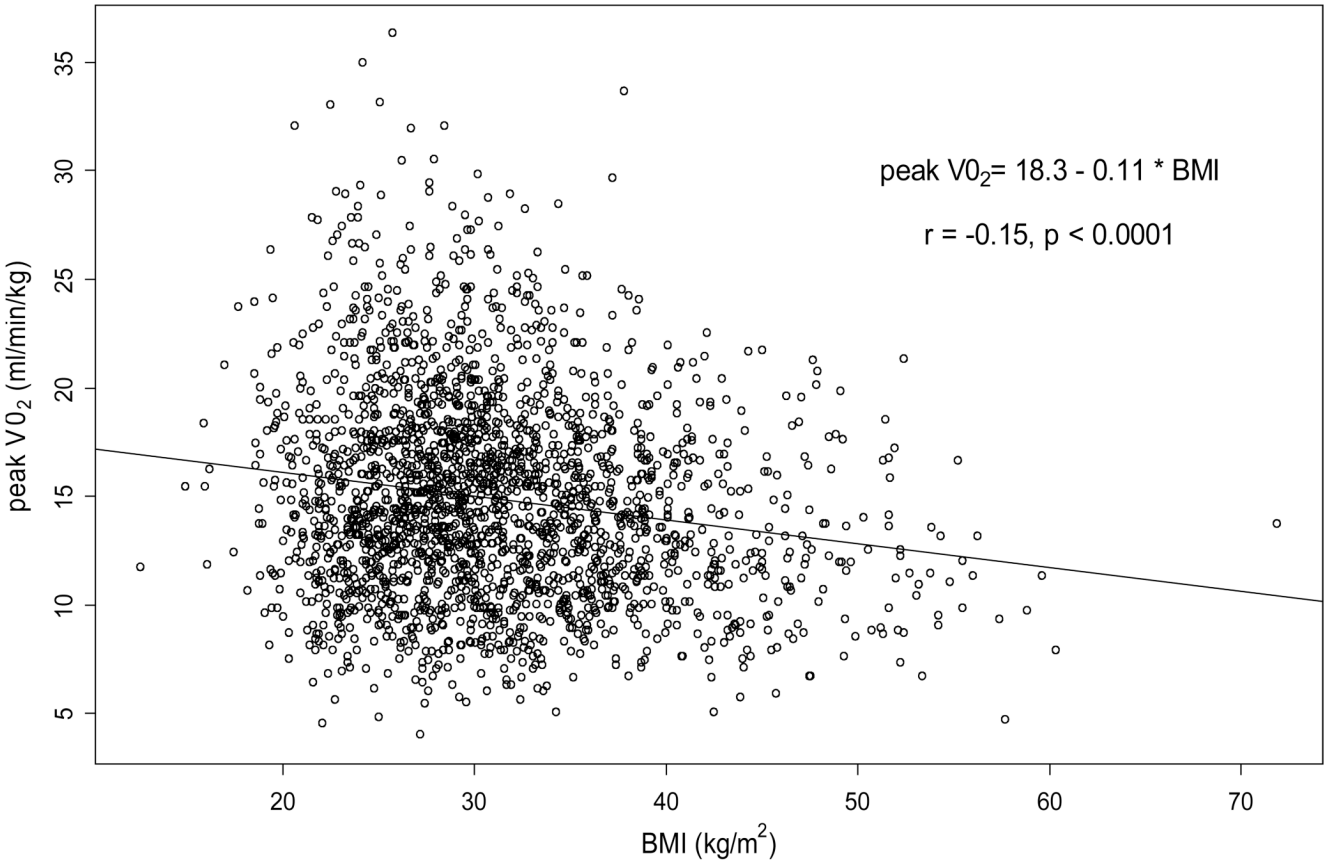

Figure 1.

1a.Scatterplot of the relationship between body mass index (BMI) and peak oxygen uptake ($PKVO_2$, mL/min).

1b.Scatterplot of the relationship between body mass index (BMI) and peak oxygen uptake ($PKVO_2$, mL/kg/min).

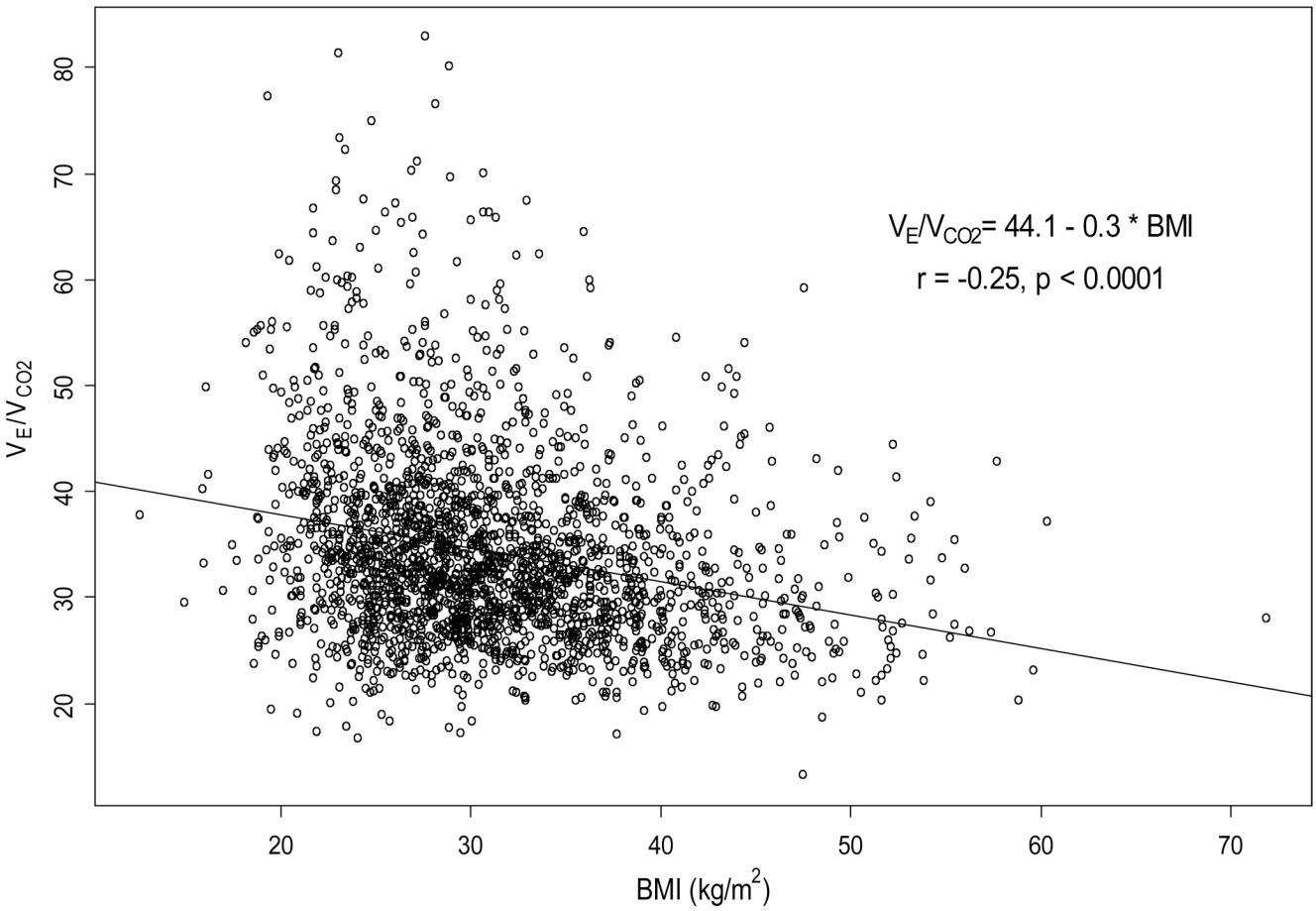

Figure 2.
Scatterplot of the relationship between body mass index (BMI) and ventilation / carbon dioxide production ratio (V_E/V_{CO2}).

Table 1

Baseline Characteristics of the Study Cohort Stratified by Body Mass Index Category

	Underweight* **N = 10**	**Normal weight N = 448**	**Overweight N = 724**	**Obese I N = 551**	**Obese II N = 330**	**Obese III N = 261**	**Pearson's r coef.****
NYHA II/III/IV %	30/70/0	63/36/1	69/30/1	63/35/2	62/37/1	51/49/0	
Left ventricular ejection fraction, %	29 (24, 34)	24 (20, 30)	25 (20, 30)	25 (21, 30)	25 (20, 31)	25 (20, 30)	0.00 (p=0.85)
Ischemic Etiology, %	40%	52%	60%	57%	44%	25%	
Beck Depression Inventory II score	14 (5, 16)	7 (4, 13)	8 (4, 13)	8 (5, 15)	10 (5, 17)	10 (6, 17)	0.12
Kansas City Cardiomyo-pathy Question-naire Overall Score	67 (49, 83)	72 (55, 88)	71 (55, 86)	66 (50, 82)	61 (47, 80)	60 (43, 76)	−0.18
EuroQOL	56 (50, 80)	70 (50, 80)	70 (56, 80)	70 (50, 80)	66 (50, 80)	65 (50, 80)	−0.07
Age (y)	61 (56, 75)	63 (55, 74)	63 (54, 70)	59 (51, 67)	56 (49, 62)	50 (40, 57)	−0.37
Sex F/M%	50/50	32/68	22/78	27/73	32/68	37/63	
Race Black/White/ other %	10/70/20	29/65/6	25/69/6	31/65/4	40/55/5	57/39/4	
Serum creatinine, mg/dL	0.8 (0.6, 0.9)	1.2 (1.0, 1.5)	1.2 (1.0, 1.5)	1.2 (1.0, 1.5)	1.1 (1.0, 1.4)	1.1 (0.9, 1.3)	−0.06 (p=0.01)
Beta-blocker, %	90%	94%	93%	95%	97%	96%	
Angiotensin-Converting Enzyme Inhibitor or Angiotensin II Receptor Blocker, %	90%	93%	94%	94%	96%	94%	

Data are recorded as median (interquartile range) for continuous variables and % total for categorical variables.

* underweight (BMI< 18.5 kg/m^2), normal weight (BMI 18.5 – 24.9 kg/m^2), overweight (BMI 25.0 – 29.9 kg/m^2), obese I (BMI 30 – 34.9 kg/m^2), obese II (BMI 35–39.9 kg/m^2), obese III (BMI ≥ 40 kg/m^2)

** Pearson's r correlation coefficient for all of the continuous variables correlated with BMI as a continuous variable. Unless otherwise indicated, all variables significant at the $p < 0.0001$ level.

Table 2

Baseline Exercise Variables Stratified by Body Mass Index Categories.

	Underweight N = 10	**Normal weight N = 448**	**Over-weight N = 724**	**Obese I N = 551**	**Obese II N = 330**	**Obese III N = 261**	**Pearson's r coef.****
Peak VO_2 (mL/min)	655 (628, 921)	962 (772, 1205)	1278 (981, 1575)	1439 (1071, 1763)	1523 (1242, 1858)	1676 (1279, 2117)	0.40
Peak VO_2 (mL/kg/min)	15.4 (11.8, 18.3)	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)	−0.17
VO_2 at VT (mL/kg/min)	13.0 (10.0, 13.6)	10.9 (9.3, 13.0)	10.8 (9.3, 12.6)	10.7 (8.7, 12.7)	10.0 (8.4, 11.6)	9.5 (8.1, 11.4)	−0.18
Peak respiratory exchange ratio	1.12 (1.00, 1.21)	1.09 (1.02, 1.17)	1.10 (1.03, 1.17)	1.09 (1.02, 1.16)	1.08 (1.02, 1.14)	1.07 (1.00, 1.13)	−0.12
O_2 pulse (mL/kg/beat)	0.13 (0.12, 0.15)	0.13 (0.10, 0.16)	0.13 (0.11, 0.15)	0.13 (0.10, 0.15)	0.11 (0.10, 0.13)	0.10 (0.08, 0.12)	−0.27
V_E/V_{CO2}	36 (33, 42)	36 (30, 43)	33 (29, 37)	32 (29, 37)	30 (27, 35)	29 (25, 34)	−0.25
Exercise time (min)	7.1 (6.0, 10.5)	9.4 (6.7, 12.0)	10.3 (8.0, 13.0)	9.8 (7.1, 12.0)	9.1 (6.6, 11.6)	8.0 (5.7, 10.3)	−0.15
6 minute walk distance (m)	362 (269, 402)	366 (296, 430)	387 (317, 446)	372 (297, 443)	362 (294, 426)	335 (274, 407)	−0.12
HR at peak exercise (beats/min)	123 (94, 139)	115 (98, 131)	119 (105, 132)	120 (103, 133)	122 (108, 136)	123 (111, 141)	0.13

Data are recorded as median (interquartile range) for continuous variables and % total for categorical variables.

* underweight (BMI< 18.5 kg/m^2), normal weight (BMI 18.5 – 24.9 kg/m^2), overweight (BMI 25.0 – 29.9 kg/m^2), obese I (BMI 30 – 34.9 kg/m^2), obese II (BMI 35–39.9 kg/m^2), obese III (BMI ≥ 40 kg/m^2)

** Pearson's r correlation coefficient for all of the continuous variables correlated with BMI as a continuous variable. All r values are significant at the $p < 0.0001$ level.

Table 3

Multivariable Analysis of Peak VO2 (mL/kg/min) as a Continuous Variable.

Variable	Coefficient	95% Confidence Interval	Partial R-square	P-value
Age	−0.13	(−0.14, −0.11)	0.12	<0.0001
BMI	−0.16	(−0.18, −0.13)	0.07	<0.0001
CPX mode (treadmill vs. bike)	−2.5	(−3.2, −1.9)	0.02	<0.0001
Diabetes	−1.2	(−1.5, −0.8)	0.02	<0.0001
ECG vent. cond.			0.03 (overall)	<0.0001 (overall)
IVCD	−1.3	(−1.8, −0.8)		
LBBB	−0.5	(−1.0, −0.1)		
Paced	−1.5	(−1.9, −1.1)		
RBBB	−1.6	(−2.5, −0.8)		
Gender	−2.1	(−2.5, −1.7)	0.06	<0.0001
LVEF	0.07	(0.05, 0.09)	0.02	<0.0001
NYHA Class (II vs. III/IV)	−2.0	(−2.4, −1.7)	0.06	<0.0001
PVD	−2.0	(−2.6, −1.4)	0.02	<0.0001
Race			0.06 (overall)	<0.0001 (overall)
African Amer.	−2.2	(−2.5, −1.8)		
Other	−1.1	(−1.8, −0.4)		
Region			0.03 (overall)	<0.0001 (overall)
West USA	0.7	(0.1, 1.2)		
Midwest USA	0.5	(0.2, 0.9)		
Northeast USA	−0.8	(−1.3, −0.2)		
Canada	−1.1	(−1.7, 0.5)		
France	2.3	(1.0, 3.6)		

Reference categories for categorical variables: sex = male, diabetes = non-diabetics, PVD = non-PVD, region = South USA, race = Caucasian, NYHA Class = Class II, CPX mode = treadmill, Overall model $R^2 = 0.39$.

Table 4

Candidate Predictor Variables for the Peak VO2 and V_E/V_{CO2} Multivariable Models

- gender
- diabetes (history of)
- stroke (history of)
- hypertension (history of)
- prior CABG
- prior valve surgery
- prior PCI
- prior MI
- peripheral vascular disease (history of)
- COPD (history of)
- depression (history of)
- atrial fib./flutter (history of)
- permanent pacemaker
- cardiac resynchronization therapy
- ACE inhibitor at baseline
- beta blocker at baseline
- etiology of heart failure
- CPX mode (treadmill or bicycle)
- heart failure hospitalizations in the last 6 months (0, 1, 2, or 3+)
- region (4 regions of US, Canada, or France)
- race (African American, White, or Other)
- NYHA class (II vs. III/IV) at baseline
- CCS angina class at baseline
- rest ECG ventricular conduction prior to baseline CPX test (normal, LBBB, RBBB, IVCD, or paced)
- rest ECG rhythm prior to baseline CPX test (sinus, a fib, or other)
- smoking status (never, current, or past)
- diastolic BP
- systolic BP
- BMI
- resting HR (clinic visit)
- resting HR (CPX test)
- LVEF
- age

Table 5

Multivariable Analysis of V_E/V_{CO2} on CPX.

Variable	Coefficient	95% Confidence Interval	Partial R-square	P-value
Age	0.14	(0.11, 0.17)	0.04	<0.0001
BMI	−0.22	(−0.27, −0.17)	0.03	<0.0001
ECG vent. cond.			0.01 (overall)	<0.0001 (overall)
IVCD	2.2	(1.1, 3.3)		
LBBB	1.3	(0.3, 2.3)		
Paced	1.9	(0.9, 2.8)		
RBBB	3.3	(1.5, 5.2)		
LVEF	−0.16	(−0.20, −0.11)	0.02	<0.0001
NYHA Class (II vs. III/IV)	3.4	(2.8, 4.2)	0.04	<0.0001

Reference categories for categorical variables: NYHA Class = Class II, ECG ventricular conduction = normal conduction

Overall model $R^2 = 0.19$.