Impact of Cardiorespiratory Fitness on the Obesity Paradox in Patients With Systolic Heart Failure

Adrienne L. Clark, MD[a], Gregg C. Fonarow, MD[b], and Tamara B. Horwich, MD, MS[b,*]

Although high body mass index (BMI) is associated with improved outcomes in established heart failure (HF), the impact of cardiorespiratory fitness on this obesity paradox is less clear. We studied 1,675 patients with systolic HF who underwent cardiopulmonary exercise testing at a single university center (77.4% men, mean age 52.2 ± 11.6 years, mean left ventricular ejection fraction 23.2 ± 7.1% and New York Heart Association class III or IV in 79.1%). We evaluated 2-year survival in patients stratified by both BMI (normal 18.5 to 24.9 kg/m^2[reference], overweight 25 to 29.9 kg/m^2, obese ≥30.0 kg/m^2) and by peak oxygen uptake ($PKVO_2$; high >14 ml/kg/minute, low ≤14 ml/kg/minute). At 2 years, BMI category was significantly associated with outcomes for the low $PKVO_2$ group ($p < 0.001$) but not the high $PKVO_2$ group ($p = 0.1$). In the low $PKVO_2$ group, obese patients had decreased risk of death free from urgent status 1A heart transplant or ventricular assist device placement after multivariate adjustment compared with normal BMI (hazard ratio [HR] 0.64, 95% confidence interval [CI] 0.44 to 0.91, $p = 0.01$); no significant difference was observed for overweight patients (HR 0.91, 95% CI 0.66 to 1.25, $p = 0.5$). In the high $PKVO_2$ group, no relation was seen (overweight BMI HR 0.75, 95% CI 0.43 to 1.32, $p = 0.3$; obese HR 0.87, 95% CI 0.43 to 1.75, $p = 0.7$). In conclusion, the obesity paradox was only observed in patients with lower cardiorespiratory fitness in this advanced systolic HF cohort, indicating that improved functional capacity may attenuate the obesity paradox. **(Am J Cardiol 2015;115:209–213)**

Obesity is a risk factor for development of heart failure (HF), but once diagnosed, high body mass index (BMI) is associated with improved outcomes in patients with established HF.[1,2] Cardiorespiratory fitness (CRF) is an important prognostic factor in HF, in which peak oxygen uptake ($PKVO_2$) below 10 to 14 ml/kg/minute in cardiopulmonary exercise testing warrants consideration for heart transplantation.[3] $PKVO_2$ is lowest in patients with HF with BMI ≥40 and not qualitatively different across other BMI categories.[4] Fitness correlates with an improved prognosis in HF and may modify the relation between obesity as indexed by BMI and survival.[5,6] The aim of this study was to evaluate the relation between BMI categories, $PKVO_2$-defined CRF, and clinical outcomes in patients with advanced systolic HF to further clarify the significance of the obesity paradox and its implications for risk assessment and optimal weight management strategies in populations with HF.

Methods

A total of 1,979 patients were referred to a single university medical center for heart transplant evaluation and underwent cardiopulmonary exercise testing from December 1984 to November 2011. Patients with left ventricular ejection fraction >40% (n = 130), those without height or weight recorded (n = 104), and those with BMI <18.5 kg/m^2 (n = 69) were excluded from the analysis. The final group consisted of 1,675 subjects. All subjects were followed in a comprehensive HF management program as previously described. Medical record review was approved by the Medical Institutional Review Board of the University of California, Los Angeles. Height and body weight were measured within 3 months of initial referral. Hemodynamic parameters and medical treatments were recorded after Swan-Ganz catheterization when necessary. Past medical history was extracted from medical record review. Cardiopulmonary exercise testing was performed on an upright cycle ergometer as previously described to obtain physiologic variables including $PKVO_2$.[7]

Patients were followed until death, urgent status 1A heart transplant, or ventricular assist device (VAD) placement. Status 1A transplant and VAD placement were censored under the assumption that these patients would have died without an intervention. All-cause mortality was analyzed as a secondary end point.

For analysis, we stratified patients by (1) BMI, normal (18.5 to 24.9 kg/m^2), overweight (25 to 29.9 kg/m^2), and obese (≥30.0 kg/m^2) and (2) CRF level, using the previously established cutoff of $PKVO_2$ >14 ml/kg/minute to identify relatively high fitness patients.[3,8,9] Continuous data are reported as mean ± SD; categorical data are shown as frequency (percentage). One-way analysis of variance was used to identify differences in continuous variables between groups; categorical variables were compared with the chi-square test. Actuarial survival curves were calculated by

[a]Department of Medicine and [b]Division of Cardiology, Department of Medicine, David Geffen School of Medicine, University of California, Los Angeles, Los Angeles, California. Manuscript received June 14, 2014; revised manuscript received and accepted October 14, 2014.

This work was supported by a research award from the Western State Affiliate, American Heart Association and the Ahmanson-UCLA Foundation (Los Angeles, California). All the authors had access to the data and a role in writing the manuscript.

See page 213 for disclosure information.

*Corresponding author: Tel: (310) 825-8816; fax: (310) 206-9111.
E-mail address: thorwich@mednet.ucla.edu (T.B. Horwich).

0002-9149/14/$ - see front matter © 2015 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.amjcard.2014.10.023

Table 1A
Differences in baseline characteristics by body mass index

Variable	Body mass index (kg/m^2)			*P* value
	18.5-24.9 (n=633)	25-29.9 (n=600)	≥30.0 (n=442)	
Age (years)	53.4 ± 12.3	53.1 ± 10.6	49.6 ± 11.4	<0.0001
Male	74.5%	82.4%	74.9%	0.001
Left ventricular ejection fraction (%)	22.9 ± 7.1	23.5 ± 7.1	23.6 ± 7.3	0.3
Body mass index (kg/m^2)	22.4 ± 1.7	27.2 ± 1.4	32.8 ± 1.9	<0.0001
Peak oxygen uptake (ml/kg/min)	13.9 ± 5.5	13.9 ± 4.8	13.1 ± 4.9	0.02
Peak oxygen uptake (ml/min)	936.3 ± 391.8	1145.6 ± 427.0	1330.5 ± 541.5	<0.0001
Coronary artery disease	43.2%	46.3%	36.8%	0.01
Left ventricular end-diastolic dimension (mm)	68.7 ± 10.6	70.1 ± 10.7	69.7 ± 11.2	0.07
Left ventricular end-diastolic dimension index (mm/m^2)	38.5 ± 6.4	35.3 ± 5.8	32.0 ± 5.8	<0.001
NYHA Class III/IV	82.8%	77.1%	76.2%	0.02
Hypertension	32.4%	43.6%	47.1%	<0.001
Diabetes mellitus	19.3%	28.4%	32.7%	<0.001
Aldosterone antagonist use	33.1%	40.5%	45.5%	<0.001
Beta blocker use	55.5%	63.6%	70.5%	<0.001

Table 1B
Differences in baseline characteristics by peak oxygen uptake

Variable	Peak oxygen uptake (ml/kg/min)		*P* value
	≤14.0 (n=1024)	>14.0 (n=651)	
Age (years)	53.8 ± 11.0	49.7 ± 11.9	<0.001
Male (%)	72.8%	84.6%	<0.001
Left ventricular ejection fraction (%)	23.2 ± 7.0	23.4 ± 7.4	0.4
Body mass index (kg/m^2)	30.3 ± 88.1	26.8 ± 5.7	0.3
Peak oxygen uptake (ml/kg/min)	10.6 ± 2.3	18.4 ± 4.5	<0.001
Peak oxygen uptake (ml/min)	874.4 ± 276.0	1494.1 ± 473.8	<0.001
Coronary artery disease	47.2%	35.4%	<0.001
Left ventricular end-diastolic dimension (mm)	69.4 ± 11.0	69.4 ± 10.4	0.9
Left ventricular end-diastolic dimension index (mm/m^2)	35.5 ± 6.7	35.6 ± 6.1	0.8
NYHA Class III/IV	85.8%	68.5%	<0.001
Hypertension	42.9%	36.4%	0.006
Diabetes mellitus	31.4%	17.8%	<0.001
Aldosterone antagonist use	41.9%	34.7%	0.003
Beta blocker use	63.5%	60.8%	0.2

the Kaplan-Meier estimate, with differences between curves calculated using the log-rank statistic. The cohort was split into high and low $PKVO_2$ groups to determine relation of BMI to event-free survival in each group. The joint impact of BMI and CRF on outcome was examined by stratifying BMI categories by CRF level resulting in 6 combined groups; high $PKVO_2$ with normal BMI was used as the reference group. Cox proportional hazards regression analysis was used to determine univariate association with mortality as well as multivariate association after adjusting for potential confounding variables. A p value <0.05 was considered statistically significant for all tests. All statistical analysis was performed using SPSS version 21.0 (IBM, Armonk, NY); Kaplan-Meier curves were generated in Prism version 6.0 (GraphPad, La Jolla, CA).

Results

Table 1A displays differences in key baseline characteristics by BMI. As BMI class increased, so did rates of hypertension, diabetes, aldosterone antagonist use, and β blockade, whereas New York Heart Association class III and/or IV disease became less common. Table 1B lists key differences between $PKVO_2$ groups; patients with higher $PKVO_2$ were younger, more likely to be men, and had lower rates of coronary disease, New York Heart Association class III and/or IV HF, hypertension, and diabetes. Table 2 presents differences in key baseline characteristics according to BMI classification in low and high $PKVO_2$ subgroups.

During 2 years of follow-up, there were 213 deaths, 147 urgent status 1A heart transplants, and 7 VAD placements. There were also 216 nonurgent (status 1B or 2) heart transplants. Annual mortality for the overall group was 10.9% (including transplant and device recipients). Patients with higher $PKVO_2$ (>14 ml/kg/minute, n = 651) had improved survival at 2 years (84.6%) compared with those with lower $PKVO_2$ (n = 1,024, 69.1% survival, p <0.001). Higher BMI was a significant predictor of improved survival in the overall cohort (Figure 1, p = 0.001) and in the low $PKVO_2$ subgroup (Figure 2, p <0.001), but not in the high $PKVO_2$ subgroup (Figure 2, p = 0.14). In combined analysis of CRF-BMI groups, high $PKVO_2$ groups had the best survival, with a persistent obesity paradox in the low $PKVO_2$ groups (Supplementary Figure 1, p <0.001).

Obese BMI carried a significantly decreased risk of death, urgent transplant, or device placement compared with normal BMI in the low $PKVO_2$ group (hazard ratio [HR] 0.52, 95% confidence interval [CI] 0.38 to 0.72, p <0.001); no significant difference was observed for overweight patients (Table 3). In the high $PKVO_2$ group, no relation was seen between BMI and survival. After adjusting for age, diabetes, ischemic HF origin, left ventricular ejection fraction, New York Heart Association class, and angiotensin-converting enzyme inhibitor and/or angiotensin receptor blocker use, this trend persisted: obese patients but not overweight patients were at significantly at lower risk compared with normal BMI subjects in the low CRF group