JACC: HEART FAILURE
VOL. 3, NO. 11, 2015

ISSN 2213-1779/$36.00
PUBLISHED BY ELSEVIER INC.
http://dx.doi.org/10.1016/j.jchf.2015.06.009

The Heart Failure Overweight/Obesity Survival Paradox

The Missing Sex Link

Amanda R. Vest, MBBS,* Yuping Wu, PhD,† Rory Hachamovitch, MD, MSc,‡ James B. Young, MD,*§ Leslie Cho, MD‖

ABSTRACT

OBJECTIVES This study sought to determine whether body mass index (BMI) has a differential impact on survival for females versus males with advanced systolic heart failure (HF).

BACKGROUND Females have a survival advantage in HF, the mechanisms of which are unclear. There is also a proposed "obesity survival paradox" in which excess adiposity promotes HF survival.

METHODS We reviewed 3,811 patients with left ventricular ejection fraction ≤40% who had undergone cardiopulmonary exercise testing between 1995 and 2011. The endpoint was all-cause mortality. Multivariable analysis was performed using a Cox proportional hazards model. Because of the nonlinearity of BMI, a restricted cubic spline was used. An interaction term was added to investigate the impact of BMI on mortality by sex.

RESULTS The unadjusted data demonstrated an overall obesity survival paradox in HF. This survival paradox disappeared for males after adjustment for potential confounders, with overweight and obese males showing higher adjusted mortality hazard ratios compared with normal weight males. Conversely, females in the overweight BMI range (25.0 to 29.9 kg/m^2) had the lowest adjusted mortality (hazard ratio: 0.84; 95% confidence interval: 0.77 to 0.93; $p = 0.0005$ compared with normal weight females) with a nadir in mortality hazard just below BMI 30 kg/m^2. The multivariable model supported a differential impact of BMI on mortality in males versus females (p for interaction <0.0001).

CONCLUSIONS In this advanced HF cohort, an unadjusted obesity survival paradox disappeared after adjustment for confounders. Overweight and obese males had higher adjusted mortality than normal weight males, whereas a BMI in the overweight range was associated with a significant survival benefit in females. (J Am Coll Cardiol HF 2015;3:917–26)

Obesity is a key determinant of cardiovascular health and an independent risk factor for the development of heart failure (HF) (1,2). The "overweight" and "obese" states are defined by body mass index (BMI), with overweightness diagnosed in the BMI range ≥25 to <30 kg/m^2 and obesity ≥30 kg/m^2. Among 59,178 adults followed for a mean of 18 years, the adjusted hazard ratios for incident HF at BMIs <25, 25 to 29.9, and ≥30 kg/m^2 were 1.00, 1.25, and 1.99 ($p < 0.001$) for men and 1.00, 1.33, and 2.06 ($p < 0.001$) for women, respectively (3). However, multiple investigators have demonstrated an "obesity survival paradox" in HF with reduced (and preserved) ejection fraction, whereby overweight and obese patients have either no increased mortality risk compared with normal weight counterparts, or even a lower mortality risk (4–10). Several potential explanations have been

From the *Kaufman Center for Heart Failure, Heart and Vascular Institute, Cleveland Clinic, Cleveland, Ohio; †Department of Mathematics, Cleveland State University, Cleveland, Ohio; ‡Section of Cardiovascular Imaging, Cleveland Clinic, Cleveland, Ohio; §Endocrinology and Metabolism Institute, Cleveland Clinic, Cleveland, Ohio; and the ‖Section of Preventative Cardiology and Rehabilitation, Cleveland Clinic, Cleveland, Ohio. This research project was conducted under the supervision of the senior author, Dr. Cho. Funding was provided by the Cleveland Clinic Women's Cardiovascular Research Center and the Karos Chair for Women's Cardiovascular Research fund. The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received February 11, 2015; revised manuscript received June 2, 2015, accepted June 12, 2015.

ABBREVIATIONS AND ACRONYMS

ACE = angiotensin-converting enzyme

AF = atrial fibrillation

ARB = angiotensin receptor blocker

BMI = body mass index

CAD = coronary artery disease

CI = confidence interval

CRF = cardiorespiratory fitness

HF = heart failure

HR = hazard ratio

HRR = heart rate recovery

HTN = hypertension

LBM = lean body mass

LVAD = left ventricular assist device

LVEF = left ventricular ejection fraction

MET = metabolic equivalent of task

NW = normal weight (18.5 to 24.99 kg/m^2)

NYHA = New York Heart Association

OB = obese (≥30 kg/m^2)

OW = overweight (25 to 29.99 kg/m^2)

RER = respiratory exchange ratio

SBP = systolic blood pressure

VE/VCO_2 = ratio of ventilation to increase in carbon dioxide output

VO_2 = oxygen uptake

Vt = tidal volume

postulated to explain these unexpected survival outcomes, including the potential confounding of cigarette smoking or undiagnosed systemic illness. There is also the possibility of "lead time bias" whereby obese individuals present with HF symptoms earlier in their disease course, or a "healthy survivor effect," whereby the most comorbid obese individuals die before developing HF, leaving the surviving obese HF patients with disproportionately favorable outcomes.

SEE PAGE 927

The paradox could alternatively be explained by the protection from cardiac cachexia afforded by baseline excess adiposity or by myocardial effects of adipokines secreted from adipose tissue. Both the biological mechanisms of the proposed paradoxical relationship between BMI and mortality in HF, and the role of sex in this relationship, remain incompletely understood. Given the female survival advantage in HF (11–13), and the recognition that female myocardium shows greater fatty acid metabolism and lower glucose utilization (14), we hypothesized that females with HF may derive a greater degree of protection from excess adiposity than males.

METHODS

STUDY POPULATION. We identified 4,380 consecutive adult patients with systolic HF who underwent cardiopulmonary exercise testing at Cleveland Clinic between January 1, 1995, and November 1, 2011. Institutional review board approval was granted both for the prospective recording of exercise testing data and the retrospective collection of additional data specific to this project; the requirement for informed consent was waived. We removed 253 patients from the cohort because of incomplete data, with either a missing stress test date (n = 4), missing mortality follow-up data (n = 46), no information in the electronic medical record to verify clinical data (n = 116), or missing key cardiopulmonary stress test parameters (n = 87). Patients with a baseline left ventricular ejection fraction (LVEF) in the 41% to 50% range were removed (n = 130) to restrict analysis to individuals with LVEF ≤40%. We filtered out patients who had received a heart transplant (n = 15) or left ventricular assist device (LVAD) (n = 8) before their stress test date. Patients with a primary valvular cardiomyopathy etiology (n = 85) or severe congenital heart disease (n = 27) were also excluded from this analysis. We also excluded 51 patients with a BMI <18.5 kg/m^2 (below the "normal weight" range). Thus, the final cohort contained 3,811 subjects. If a patient underwent multiple cardiopulmonary stress tests, only the initial test was considered.

Baseline characteristics were prospectively recorded in the stress test database by the exercise physiologist conducting the test. Parameters such as HF etiology, presence of coronary artery disease (CAD), diabetes status, smoking status, and HF medications were ascertained by the physiologist through a combination of verbal history-taking and medical chart review. The patient's weight was always measured on the day of the test. Smoking and medication status were documented as current at the time of the test. The presence of CAD was defined as a prior myocardial infarction or any degree of obstruction on coronary imaging. Retrospective chart review was performed for >20% of database subjects to confirm the accuracy of the prospectively entered data.

CARDIOPULMONARY EXERCISE TESTING. Symptom-limited exercise stress testing was conducted by trained exercise physiologists and supervised by a physician. Exercise testing was performed using a treadmill stress in the majority of patients; the alternate option was a stationary bike. The exercise physiologist assigned the patient to the Bruce, modified Bruce, Cornell 0%, Cornell 5%, Cornell 10%, Naughton, or modified Naughton protocols, appropriate to the patient's physical abilities. Gas exchange data were collected throughout the test using a MedGraphics cardiopulmonary metabolic cart (St. Paul, Minnesota). Heart rate targets were not used as an endpoint or to judge the adequacy of the test. Blood pressure was manually measured every minute and the heart rate was recorded from an electrocardiogram printed each minute during the test. Electrocardiographic changes and symptoms were also recorded at the end of each stage. Heart rate recovery (HRR) was calculated as peak exercise heart rate minus the heart rate at 1 minute post-exercise. A standard walking cool-down was used during recovery.

The oxygen consumption (VO_2) was averaged over 30-s intervals throughout the test and the peak VO_2 was determined as the highest 30-s interval in the last 2 min of the test. The ventilatory threshold was defined as the VO_2 at which expired carbon dioxide increased nonlinearly relative to VO_2 (V-slope method). The ratio of the increase in ventilation to the increase in CO_2 output (VCO_2) was recorded at peak exercise (15). Estimated functional capacity was