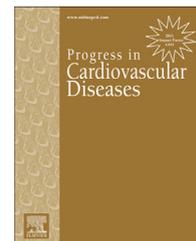


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## Obesity and the Obesity Paradox in Heart Failure

Adrienne L. Clark<sup>a</sup>, Gregg C. Fonarow<sup>b</sup>, Tamara B. Horwich<sup>b,\*</sup>

<sup>a</sup>Department of Medicine, David Geffen School of Medicine, University of California, Los Angeles, CA

<sup>b</sup>David Geffen School of Medicine, University of California, Los Angeles, CA

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### ABSTRACT

Obesity is a growing public health problem in the general population, and significantly increases the risk for the development of new-onset heart failure (HF). However, in the setting of chronic HF, overweight and mild to moderate obesity is associated with substantially improved survival compared to normal-weight patients. Evidence exists for an “obesity paradox” in HF, with the majority of data measuring obesity by body mass index, but also across various less-frequently used measures of body fat (BF) and body composition including waist circumference, waist-hip ratio, skinfold estimates of percent BF, and bioelectrical impedance analysis of body composition. Other emerging areas of investigation such as the relationship of the obesity paradox to cardiorespiratory fitness are also discussed. Finally, this review explores various explanations for the obesity paradox, and summarizes the current evidence for intentional weight loss treatments for HF in context.

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### Prevalence of obesity in general and HF populations

Obesity is a growing public health problem in the United States and worldwide. Between 1960–1962 and 2009–2010 the percentage of obese patients as identified by body mass index (BMI) in the U.S. National Health and Nutrition Examination Survey nearly tripled, from 13.4% of patients with BMI  $\geq 30$  kg/m<sup>2</sup> and 0.9% with BMI  $\geq 40$  kg/m<sup>2</sup> initially, to 36.1% with BMI  $\geq 30$  kg/m<sup>2</sup> and 6.6% with BMI  $\geq 40$  kg/m<sup>2</sup> in the most recent study period.<sup>1</sup> During this time, the percentage of overweight (BMI 25.0–29.9 kg/m<sup>2</sup>) remained stable at approximately one-third of the population, meaning that the distribution of BMI in the U.S. has now drastically shifted toward higher values. Overweight and obesity, as defined by BMI, are highly prevalent in heart failure (HF) populations as well. While prevalence varies by population studied, 32%–49% of HF patients are obese (BMI  $\geq 30$  kg/m<sup>2</sup>) and 31%–40% are overweight (BMI 25.0–29.9 kg/m<sup>2</sup>).<sup>2,3</sup> Of note, obesity is significantly more prevalent in HF patients

with preserved ejection fraction as compared to those with reduced ejection fraction.<sup>4</sup>

### Obesity as a risk factor for HF

Obesity as measured by elevated BMI is a major risk factor for the development of HF. Among 5,81 patients in the Framingham Heart Study, BMI was found to correlate with HF risk in a dose-dependent fashion: HF risk increased by 5% for men and 7% for women for each single-unit increase in BMI, even after adjustment for demographics and other known risk factors such as diabetes, hypertension, and cholesterol.<sup>5</sup> This positive correlation between BMI and HF risk for both overweight and obese was confirmed in the larger Physicians' Health Study of 21,094 men without known coronary artery disease, where overweight participants had a 49% increase in HF risk compared with lean participants and obese participants had a 180% increase (95% CI, 124–250).<sup>6</sup>

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\* Address reprint requests to Tamara B. Horwich, MD, MS, University of California, 10833 Le Conte Ave CHS A2-237, Los Angeles, CA 90095. E-mail address: [thorwich@mednet.ucla.edu](mailto:thorwich@mednet.ucla.edu) (T.B. Horwich).

### Abbreviations and Acronyms

BIA = bioelectrical impedance analysis
BF = body fat
BMI = body mass index
CRF = cardiorespiratory fitness
DEXA = dual-energy x-ray absorptiometry
EATE = epicardial adipose tissue
HF = heart failure
WC = waist circumference

These same trends have been demonstrated in non-U.S. populations. A study of 59,178 participants demonstrated the graded link between BMI and HF risk, with multivariable-adjusted hazard ratios of HF for normal, overweight, and obese BMI of 1.00, 1.25, and 1.99 for men and 1.00, 1.33, and 2.06 for women, respectively.<sup>7</sup> Levitan and colleagues<sup>8</sup>

analyzed two population-based prospective cohorts of 80,630 Swedish men and women; not only higher BMI but higher waist circumference (WC), waist-hip ratio, and waist to height ratio were associated with higher risk of HF hospitalization and mortality.

### Evidence for an obesity paradox in HF

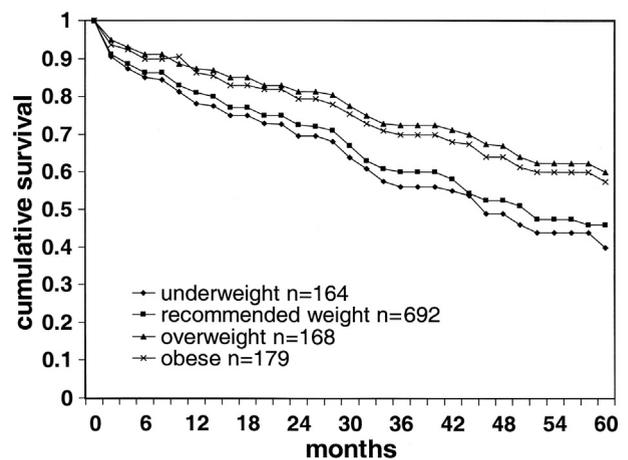
Although elevated BMI is well established as a risk factor for HF, a surprising relationship between BMI and outcomes in those with established HF has been observed. Obesity as measured by BMI and various other indices has been linked to improved HF survival in observational studies. This counter-intuitive epidemiologic association between survival outcomes and traditional risk factors, reverse epidemiology or “obesity paradox,” has now been well documented in numerous studies in the HF medical literature. It was first described by Horwich et al.<sup>9</sup> in 2001 in a cohort of 1203 advanced systolic HF patients followed at a single university transplant center, where patients with higher BMI ( $>27.8 \text{ kg/m}^2$ ) were found to have significantly improved risk-adjusted, transplant-free survival (Fig 1). The worst outcomes were seen in the underweight group, followed closely by normal-weight HF patients. A subsequent analysis of 7767 stable outpatients with chronic HF enrolled in the Digitalis Intervention Group also revealed lower risk-adjusted mortality rates in the overweight and obese compared to normal-weight patients, with hazard ratios of 0.88 (0.80–0.96) and 0.81 (0.72–0.92), respectively.<sup>10</sup> Another large, randomized controlled trial of 7599 patients with symptomatic HF with either reduced or preserved systolic function showed that patients in lower BMI categories (underweight and normal weight) had a graded increase in the risk of death; the group with the highest BMI ( $>35 \text{ kg/m}^2$ ) had similar risk to those with a BMI of 30.0–34.9  $\text{kg/m}^2$ .<sup>2</sup> Larger investigations such as a meta-analysis of nine observational HF studies ( $n = 28,209$ ) by Oreopoulos et al.<sup>11</sup> also found that overweight and obese individuals respectively had reduced cardiovascular (–19% and –40%, respectively) and all-cause (–16% and –33%) mortality during 2.7 years of follow-up as compared with those without elevated BMI. Another analysis of BMI and its relationship to in-hospital mortality for 108,927 patients with

decompensated HF identified a 10% reduction in mortality for every 5-unit increase in BMI ( $P < 0.001$ ).<sup>12</sup>

Most studies of the obesity paradox have used BMI to estimate body composition and identify overweight and obese patients, for reasons of widespread acceptance and ease of use. However, the reliability of BMI as a measure of adiposity has been questioned. Numerous alternate techniques may be more accurate to define obesity, including the currently clinically used waist circumference (WC), waist-hip ratio, skinfold estimates of percent body fat (BF), and bioelectrical impedance analysis (BIA) of body composition. Dual-energy x-ray absorptiometry (DEXA) is useful for assessment of BF and body compartments, but has limited application due to expense and required technical expertise.<sup>13,14</sup> The current gold standards for assessing body composition are computed tomography (CT) and magnetic resonance imaging (MRI), which are thought to provide the most reliable information on internal adipose tissue depots and lean mass, but application of these methods are also limited by expense.<sup>15</sup>

WC is a simple and inexpensive way to assess for abdominal obesity, and an established predictor of cardiovascular risk in the general population.<sup>16,17</sup> Not only higher BMI but also higher WC has been shown to be associated with improved outcomes in both men and women with advanced HF. In fact, patients with both overweight or obese BMI and high WC (defined as  $\geq 88 \text{ cm}$  in women and  $\geq 102 \text{ cm}$  in men) had the best survival in a cohort of advanced systolic HF patients at a university transplant referral center.<sup>18,19</sup>

A study of 209 HF patients used the average of three skinfolds to measure BF (thigh, chest, and abdomen skin folds in men; thigh, triceps, and suprailliac in women).<sup>20</sup> Increased percent body fat independently predicted better event-free survival in a linear fashion: every 1% absolute increase in



**Fig 1 – Risk-adjusted survival curves for the four body mass index (BMI) categories at 5 years. The variables entered into the equation were age, gender, hypertension, diabetes mellitus, left ventricular ejection fraction, hemodynamic variables, peak  $\text{VO}_2$ , mitral regurgitation, tricuspid regurgitation, medications and serum sodium, creatinine and lipid levels. Survival was significantly better for the overweight and obese BMI categories. (Adapted from Horwich et al.,<sup>9</sup> with permission from Elsevier.)**

percent BF measured via skinfold thickness was associated with a >13% reduction in major clinical events ( $P = 0.002$ ). Those patients in the highest BF quintile (mean 37.7%) had the lowest rate of death/urgent heart transplant (5%), compared to an event rate of 22% in the patients in the lowest body fat quintile (mean 16.4%).

BIA is also a noninvasive and reproducible technique to evaluate changes in body composition, although not widely available in the clinical setting.<sup>21</sup> In a community-based study in the United Kingdom, 1025 patients with chronic HF underwent BIA; percent BF, fat mass, and fat-free mass were associated with increased risk and percent BF was a significant predictor of mortality in a multivariable model ( $P = 0.04$ ).<sup>22</sup> A recent study found BIA to be safe for use with pacemakers and defibrillators, broadening its potential use in advanced HF populations.<sup>23</sup>

Visceral fat deposited around the heart is known as epicardial adipose tissue (EAT), which can be imaged with CT or MRI. Increased EAT is associated with insulin resistance, central adiposity, dyslipidemia, and decreased adiponectin levels from this biochemically active organ.<sup>24,25</sup> Data from both the Framingham Heart Study and Multi-Ethnic Study of Atherosclerosis reveal that in general populations, EAT is linked to both metabolic syndrome and increased cardiovascular disease burden.<sup>26,27</sup> However, early studies show that HF is associated with reduced EAT: In one study of 41 patients with HF, the HF group had less EAT as measured by MRI compared to 16 age-matched controls without established cardiac disease and low cardiac risk scores.<sup>28</sup> Furthermore, in another study HF patients with more severe disease have lower levels of EAT, with a stepwise decrease with disease progression: patients with worse LVEF (<35%) had significantly decreased EAT compared to patients with an LVEF of 35%–55% ( $P < 0.05$ ).<sup>29</sup> This relationship was independent of BMI. While this is a newer area of investigation, decrease in EAT was associated with statistically significant higher risk of HF mortality ( $P = 0.02$ ), possibly representing a novel component of the obesity paradox.<sup>28</sup>

### Extremes of body weight: cachexia and severe obesity in HF

Cachexia, or progressive weight loss with body composition alterations and disturbed homeostasis of several body systems, is a poorly understood syndrome that carries a devastating prognosis in HF and other disease states. In one HF population, 50% of those with cachexia (defined as non-intentional documented weight loss of at least 7.5% of previous normal weight over 6 months) had died at 18-month follow-up (HR 3.73, 95% CI 1.93–7.23 compared to those without cachexia).<sup>30</sup> While the cause of cachexia is unclear, a recent paper demonstrated more right ventricle dysfunction in those with cachexia and lower fat/lean body mass ratio, suggesting an association between poor right ventricular function and cachexia and highlighting the possible protective roll of adipose tissue in HF.<sup>31</sup>

However, more severe obesity may impact prognosis. One study from the Cleveland Clinic demonstrated that patients

with class III obesity (BMI  $\geq 40$  kg/m<sup>2</sup>) experienced the highest all-cause mortality/transplant (hazard ratio 2.46; 95% CI 1.4–4.30), far greater than that of the non-obese group [hazard ratio (HR) 1.44; 95% CI 1.09–1.91], when both groups were compared to obese study participants.<sup>32</sup> This mirrors findings in the general population, where a meta-analysis of 2.9 million individuals and >270,000 deaths by Flegal et al.<sup>33</sup> demonstrated “optimal” survival in the overweight group (BMI 25–29.9 kg/m<sup>2</sup>; HR 0.94, 95% CI 0.91–0.96) and class I obesity group (BMI 30–34.9 kg/m<sup>2</sup>; HR 0.95, 95% CI 0.88–1.01), compared to impaired survival in groups with class II and III obesity (HR 1.29, 95% CI 1.18–1.41). It is possible that severely obese patients with HF may benefit from different weight loss goals more so than their overweight and less obese counterparts.

### The obesity paradox in women with HF

Given the heterogeneity of those affected by HF, recent studies have made efforts to better characterize the obesity paradox in specific subgroups. Because systolic HF is more common in men, the majority of research has been conducted in predominantly male populations. This selection bias extends into studies of the obesity paradox in HF despite accepted variations in fat distribution by sex: women may make up as little as 13% of a study population or sex of participants may not be reported.<sup>34,35</sup> One investigation identified BMI <25 kg/m<sup>2</sup> and normal WC (<102 cm in men and <88 cm in women) as strong independent predictors of increased mortality in men (relative risk for BMI 1.34, 95% CI 1.13–1.58; WC 2.02, 1.18–3.45).<sup>19</sup> However, only BMI was significant for the subgroup of women (1.38, 1.02–1.89). This study may have been limited by small sample size ( $n = 469$  with recorded WC), pointing to the need for further investigation of HF outcomes in women.

### The obesity paradox, cardiorespiratory fitness, and HF prognosis

Cardiorespiratory fitness (CRF), measured variously as peak oxygen uptake (VO<sub>2</sub>) or minute ventilation (V<sub>E</sub>)/carbon dioxide production (VCO<sub>2</sub>), has been identified as an important predictor of survival in HF.<sup>36,37</sup> Chase et al.<sup>36</sup> studied a cohort of 744 HF patients and found that while patients with obese BMI had significantly lower V<sub>E</sub>/VCO<sub>2</sub> slopes than patients in normal- and overweight BMI groups, ultimately V<sub>E</sub>/VCO<sub>2</sub> was a strong independent predictor of improved survival irrespective of BMI. Lavie et al.<sup>38</sup> later demonstrated that CRF level may actually modify the obesity paradox: in 2066 patients with systolic HF, BMI was a significant predictor of age- and sex-adjusted survival in the group with low peak VO<sub>2</sub> (<14 mL/O<sub>2</sub>/kg) ( $P = 0.03$ ), but not in the high-CRF group. These findings indicated that favorable scores in core components of cardiorespiratory exercise testing might mitigate or even negate the impact of the obesity paradox in HF, and that exercise training to improve CRF is reasonable even for the less obese. Additional studies of the interaction

between body composition and CRF may provide a better understanding of the obesity paradox in HF.

### Proposed explanations for the obesity paradox

Various competing and often contradictory mechanisms have been proposed for the HF obesity paradox (Table 1). HF is a catabolic state, and overweight and obesity may represent metabolic reserve while patients at lower BF levels may suffer from unintentional weight loss resulting in “cardiac cachexia,” known to be associated with a poor prognosis.<sup>39,40</sup> Obese patients may also experience greater functional impairment and have more impaired quality of life in part from their increased body mass, and thus present earlier in their disease course. This association of obesity with better outcomes in patients with established HF may represent survival bias, index event bias, or reverse causation.

Obesity is linked to lower circulating levels of B-type natriuretic peptide, which may also lead to earlier symptomatology and presentation.<sup>41</sup> These patients are also thought to have a beneficial attenuated response to the renin–angiotensin–aldosterone system, yet at the same time can maintain higher blood pressures, which may preserve renal function and permit them to tolerate more and higher doses of cardioprotective medications such as beta-blockers, angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, and diuretics.<sup>42</sup> Obese patients may also benefit from the protective effects of various anti-inflammatory adipokines, including soluble tumor necrosis factor- $\alpha$  receptor, which would neutralize some component of the inflammatory process of their disease.<sup>43,44</sup>

As discussed, given the limitations of various indices of BF, it is also quite plausible that some of the patients identified as “obese” may actually have increased muscle mass and muscular strength compared to their “normal-weight” counterparts.<sup>14</sup> BMI may not accurately distinguish between percent BF and lean mass, and the relationship between BMI and BF varies with age, sex, and ethnicity.<sup>45–47</sup> The accuracy of BMI in identifying obesity appears to be particularly limited in the intermediate BMI ranges, as well as in men and in the elderly. This is important because the obesity paradox was

first identified in these intermediate ranges of BMI (overweight individuals) and because white men make up the majority of most HF study cohorts.<sup>9</sup> Furthermore, obesity is a heterogeneous condition. Increased visceral fat depots have been linked to metabolic derangements such as insulin resistance, hypertriglyceridemia, low high-density lipoprotein, and elevated low-density lipoprotein, whereas obese patients with low levels of visceral adipose tissue and increased subcutaneous or gluteofemoral obesity had “normal” metabolic risk profiles.<sup>48,49</sup> The suggestion that higher lean mass may be protective is bolstered by the recent findings discussed above that obesity paradox is not strongly observed in those patients with greater levels of CRF.<sup>38</sup>

### Intentional weight loss in HF

Obesity causes hemodynamic changes and cardiac structural remodeling, the best treatment for which is intentional weight loss.<sup>50</sup> Weight reduction decreases left ventricular mass, lowers arterial pressures and left- and right-sided cardiac filling pressures, and decreases systemic oxygen consumption and cardiac output.<sup>51</sup> Despite the benefit of weight loss in the prevention of HF and other cardiac disease, weight loss recommendations for other populations may not be appropriate for HF, and there are currently no clear consensus guidelines regarding weight management in HF. The European Society of Cardiology recommends management of overweight and obese patients with HF as per guidelines for general cardiovascular disease prevention, but acknowledges the gaps in evidence.<sup>52</sup> The American College of Cardiology and American Heart Association Heart Failure clinical practice guidelines acknowledge the lack of evidence and do not make a recommendation.<sup>53</sup>

A small group of studies on diet, exercise, and bariatric surgery in patients with obesity and HF have been performed, but have been generally small, short term, and inconclusive. Evangelista et al.<sup>54</sup> randomized 14 HF patients with systolic HF, elevated BMI ( $\geq 27$  kg/m<sup>2</sup>) and type 2 diabetes to 12 weeks of a high-protein diet, standard protein diet, or control. Both intervention groups achieved weight loss, reduction in HF symptoms, and improvement in quality of life, although greatest reductions in waist circumference and percent BF were seen with the high-protein diet. However, neither group experienced change in cardiac structure or function. Another study randomized 20 systolic HF patients to 12 weeks of a portion-controlled diet, walking program, and educational sessions versus no intervention, but found no significant differences in weight or other metabolic, biomarker, or functional parameters between groups.<sup>55</sup> Both interventions were well tolerated, suggesting that larger-scale investigations are safe for obese HF groups; however, there was no difference in physical exam, laboratory values, quality of life questionnaire, 6-minute walk, or brachial ultrasound between the two groups. Likewise, the HF-ACTION study demonstrated that moderate levels of exercise were both safe and associated with nonsignificant reductions in all-cause mortality and hospitalization in relatively fit HF patients across BMI categories, although no association with weight loss was identified.<sup>3</sup> However, exercise was significantly associated with improved

**Table 1 – Proposed explanations for the obesity paradox in heart failure.**

Nonpurposeful weight loss
Greater metabolic reserves
Less cachexia
Protective cytokines or adipokines
Earlier presentation due to symptomatology
Attenuated response to renin–angiotensin–aldosterone system
Higher blood pressure leading to more optimized cardioprotective medications
Different etiology of heart failure
Increased muscle mass and muscular strength in those with high body mass index
Implications related with cardiorespiratory fitness

Adapted from Lavie et al.,<sup>34</sup> with permission from Elsevier.

quality of life.<sup>56</sup> While severe HF is generally considered a contraindication to bariatric surgery, one small retrospective analysis of 12 morbidly obese patients (BMI  $53 \pm 7$  kg/m<sup>2</sup>) with systolic HF demonstrated significant 1-year reductions in hospitalization and NYHA class as compared to matched controls, and improvement in LVEF from  $21.7\% \pm 6.5\%$  to  $35.0\% \pm 14.8\%$  ( $P < 0.01$ ).<sup>57</sup> Similarly, another retrospective investigation at the same center showed that 14 systolic HF patients who underwent bariatric surgery experienced significant improvements in BMI and LVEF over a 6-month period (from  $50.8 \pm 2.04$  kg/m<sup>2</sup> to  $36.8 \pm 1.72$  kg/m<sup>2</sup> and from  $23\% \pm 2\%$  to  $32\% \pm 4\%$ , respectively).<sup>58</sup>

Given the current state of the evidence and expert recommendations, it is reasonable to state that weight loss should not be the primary therapeutic goal for overweight and obese HF patients, but that diets aimed at mild to moderate weight loss may be reasonable in severely obese patients with the goal of weight stabilization or mild weight reduction with the aim of improving quality of life or alleviating other medical conditions. However, there is a clear need for larger, prospective studies evaluating long-term safety, efficacy, and any potential survival benefit of intentional weight modification with diet, exercise, or bariatric surgery.

## Conclusions

The association of obesity and improved survival in HF patients is well established across multiple measures of adiposity. However, more complete understanding of this relatively robust survival benefit is needed and thus calls for further investigation. Better characterization of the role of visceral and ectopic fat depots and their biochemical activity will be important in developing a complete understanding of the underlying pathophysiology. A better understanding of the role of CRF may lead to better risk assessment. Furthermore, while intentional weight loss is known to improve hemodynamic function and cardiac structure in non-HF patients, further research is needed to generate evidence-based guidelines for weight management in established HF.

## Statement of Conflict of Interest

All authors declare that there are no conflicts of interest to report.

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