

Risks and Benefits of Weight Loss in Heart Failure



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KEYWORDS

• Obesity • Heart failure • Cardiovascular disease • Weight loss

KEY POINTS

- Obesity adversely affects many cardiovascular disease (CVD) risk factors and increases the risk of most CVD, including heart failure (HF).
- However, obese patients with HF have a better prognosis than lean patients with HF, which has been termed the *obesity paradox*.
- Current data support efforts at purposeful weight loss, particularly in individuals with more severe degrees of obesity (class III) and many with class II obesity.
- Incorporating physical activity, exercise training, and cardiorespiratory fitness into purposeful weight loss seems to be a particularly attractive option for patients with HF.

INTRODUCTION

Obesity is both a risk factor and a direct causal factor for the development of heart failure (HF), because of the variety of adverse hemodynamic changes in obesity that lead to adverse cardiac remodeling and ventricular dysfunction.^{1–3} Overweight and obesity have been implicated as major risk factors for hypertension and coronary heart disease (CHD), which are 2 of the strongest risk factors related to the development of HF. Additionally, because obesity has adverse effects on cardiac structure and left ventricular (LV) systolic and, especially, diastolic function,^{1–4} it is also a powerful risk factor for the development of HF.

However, despite the well-known strong association between overweight/obesity and major cardiovascular disease (CVD) risk factors for HF, numerous studies, including those in patients with established HF, have demonstrated an “obesity paradox,” in that overweight and obese patients with HF have a more favorable clinical prognosis than do their leaner counterparts with the same degree of HF.¹

This article reviews the adverse effects of weight gain and obesity on cardiac structure and function, and on the prevalence and functional classification of HF, and discusses the benefits and risks of weight loss in patients with established HF.

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Impact of Obesity on Hemodynamic Parameters

Considerable evidence demonstrates the adverse impact of weight gain and obesity on central and peripheral hemodynamics (**Box 1, Fig. 1**).¹⁻³ An early study by Alexander and colleagues⁵ showed

Box 1

Effects of obesity on cardiac performance

- A. Hemodynamics
 1. Increased blood volume
 2. Increased stroke volume
 3. Increased arterial pressure
 4. Increased LV wall stress
 5. Pulmonary artery hypertension
- B. Cardiac structure
 1. LV concentric remodeling
 2. LV hypertrophy (eccentric and concentric)
 3. Left atrial enlargement
 4. RV hypertrophy
- C. Cardiac function
 1. LV diastolic dysfunction
 2. LV systolic dysfunction
 3. RV Failure
- D. Inflammation
 1. Increased C-reactive protein
 2. Overexpression of tumor necrosis factor
- E. Neurohumoral
 1. Insulin resistance and hyperinsulinemia
 2. Leptin insensitivity and hyperleptinemia
 3. Reduced adiponectin
 4. Sympathetic nervous system activation
 5. Activation of renin-angiotensin-aldosterone system
 6. Overexpression of peroxisome proliferator-activator receptor
- F. Cellular
 1. Hypertrophy
 2. Apoptosis
 3. Fibrosis

Abbreviations: LV, left ventricular; RV, right ventricular.

From Lavie CJ, Alpert MA, Arena R, et al. Impact of obesity and the obesity paradox on prevalence and prognosis in heart failure. *JACC Heart Fail* 2013;1:96; with permission.

a positive correlation between degree of overweight on total blood volume, stroke volume (SV), and cardiac output (CO), all increasing with weight gain. Fat-free or nonosseous mass may have contributed to the alterations, because augmentation of total blood volume and CO cannot be accounted for by excess fat mass alone.¹⁻³ Typically, the heart rate in obese does not differ appreciably from that predicted for ideal body weight. In more severe obesity, oxygen consumption (V_{O_2}), CO, SV, right ventricular (RV) end-diastolic pressure, peripheral vascular resistance, mean pulmonary artery pressure, and mean arterial pressure exceeded that predicted for patients with normal weight. Conversely, systemic vascular resistance in obesity is lower than expected based on the level of arterial blood pressure (BP).¹⁻³ In patients with class III obesity (body mass index [BMI] ≥ 40 kg/m²), exercise increased central blood volume and LV end-diastolic BP by 20% and 50%, respectively.⁶

Impact of Obesity on Cardiac Structure

The impact of obesity on LV structure and LV hypertrophy (LVH) is confounded by the inclusion of the effects of CHD and hypertension.¹⁻³ In class III obesity, heart weight, LV wall thickness, and LVH are all increased with variable effects on RV hypertrophy. However, even in normotensive class III obesity without known CHD, the obese had marked abnormalities in LV structure. In a Framingham Heart Study (n = 3922), Lauer and colleagues⁷ found that BMI correlated positively with LV wall thickness, LV internal diastolic dimension, and LV mass, even after adjusting for BP and age. Virtually all of the studies assessing patients with different degrees of obesity demonstrate that LV internal diastolic dimension (or LV diastolic volume), LV wall thickness, and LV mass index were significantly greater in obese versus lean patients. Although early studies indicate that most obese patients have eccentric LVH, more recent studies indicate that obese patients, especially with elevated BP and hypertension, also have a high prevalence of concentric LVH or LV concentric remodeling.¹⁻⁴

Obesity and Left Ventricular Function

The development of LVH in obesity, with or without elevated BP and hypertension, could predispose patients to LV diastolic dysfunction.¹⁻⁴ Thus, hemodynamic studies, especially in more severe obesity, have typically reported elevated levels of LV end-diastolic BP. In one Doppler echocardiographic study, LV diastolic dysfunction occurred in 12% of patients with class I obesity (BMI,

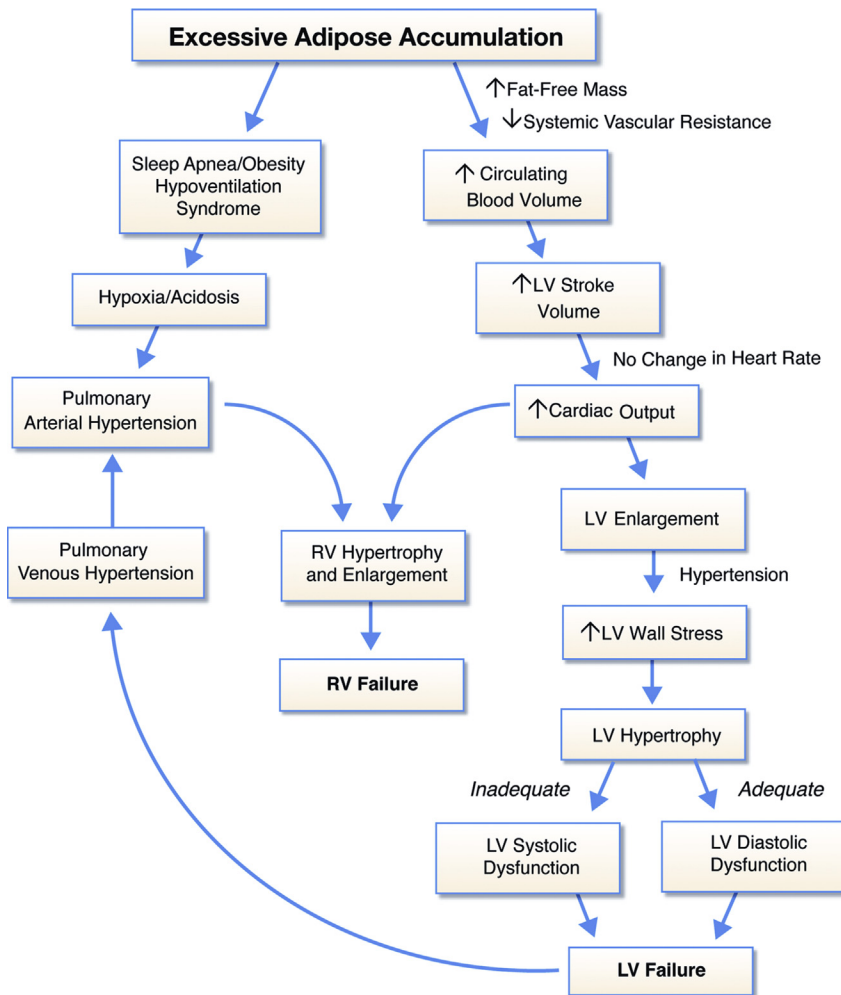


Fig. 1. The central hemodynamic, cardiac structural abnormalities and alterations in ventricular function that may occur in patients with severe obesity and predispose them to HF. LV hypertrophy in severe obesity may be eccentric or concentric. In uncomplicated (normotensive) severe obesity, eccentric LV hypertrophy predominates. In patients with severe obesity with long-standing systemic hypertension, concentric LV hypertrophy is frequently observed and may occur more commonly than eccentric LV hypertrophy. Whether and to what extent metabolic disturbances such as lipotoxicity, insulin resistance, leptin resistance, and alterations of the renin-angiotensin-aldosterone system contribute to obesity cardiomyopathy in humans is uncertain. RV, right ventricular. (From Lavie CJ, Alpert MA, Arena R, et al. Impact of obesity and the obesity paradox on prevalence and prognosis in heart failure. *JACC Heart Fail* 2013;1:95; with permission.)

30.0–34.9 kg/m²), 35% with class II obesity (BMI, 35.0–39.9 kg/m²), and 45% with class III, or “morbid,” obesity.⁸ Many other Doppler and radio-nuclide angiographic studies have confirmed the adverse effects of obesity on LV diastolic abnormalities.^{1–4}

Most studies in obese subjects have shown no significant impact of excess adipose accumulation on systolic LV function.^{1–3} If obese subjects had a lower LV systolic function than lean subjects, the differences were generally small, and LV ejection

phase indices typically remain within the normal range. Recent studies that used tissue Doppler imaging of the mitral annulus indicate a progressive decline in peak myocardial systolic velocities with increasing degrees of obesity, with more abnormal myocardial strain and strain rate being detected more commonly in obese subjects.⁹ Although early in obesity diastolic dysfunction seems to predominate over systolic dysfunction, severe obesity also demonstrates subtle abnormalities in systolic ventricular function.^{1–4}

Mechanisms of Abnormal Cardiac Structure and Function in Obesity

The increased volume with uncomplicated obesity would be expected to produce eccentric LVH.¹⁻⁴ However, obese patients also have concentric LV remodeling and concentric LVH, which may be related with elevations in BP/hypertension, activation of the sympathetic nervous system (SNS) and renin angiotensin-aldosterone system (RAAS), and effects of growth factors, such as insulin-like growth factor.^{2,3}

A variety of metabolic abnormalities may also contribute to the LV diastolic and/or systolic dysfunction, and to the LVH. Obese patients have evidence of lipotoxicity and lipoapoptosis, insulin resistance, hyperinsulinemia, and activation of the SNS and RAAS, and reduced levels of adiponectin. Although these abnormalities are clear in animal models of obesity, their relative and combined impact in humans remain uncertain and could be considered meager.^{2,3}

Obesity and Heart Failure Prevalence

In a study of 74 morbidly obese patients by Alpert and colleagues,¹⁰ nearly one-third had clinical evidence of HF, with the probability of HF markedly increasing with longer duration of morbid obesity, reaching prevalence rates exceeding 70% and 90% at 20 and 30 years of morbid obesity, respectively. In a study of 550 subjects without diabetes from Greece, however, BMI was not associated with HF risk, whereas metabolic syndrome was associated with a 2.5-fold higher risk of HF.¹¹ In contrast to patients of normal weight with metabolic syndrome, however, obese subjects without metabolic risk factors had a decreased risk of HF.

The best and probably largest study to assess the risk of obesity on future development of HF comes from the Framingham Heart Study participants.¹² This study of 5881 subjects demonstrated that for every 1 kg/m² increase in BMI, the risk of HF during a 14-year follow-up increased by 5% in men and 7% in women, respectively, with progressive increases in the risk of HF across all BMI categories.¹²

Obesity and Heart Failure Prognosis

Obesity adversely affects both systolic and, especially, diastolic ventricular function and increases the prevalence of HF. However, numerous studies and meta-analyses have shown that those who are overweight and obese with HF seem to have a better prognosis than do their leaner counterparts, a phenomenon termed the *obesity paradox*. This topic has been reviewed in detail elsewhere.¹

Briefly, although generally this paradox has been demonstrated mostly with BMI criteria, which is potentially flawed because BMI assesses both fat mass and nonfat mass, including skeletal and muscle mass, the obesity paradox has also been demonstrated with body fat, and with central obesity/waist circumference (WC).^{1,13-15} In a study of 209 patients with advanced systolic HF, Lavie and colleagues¹³ showed that for every 1% increase in percent body fat, a 13% independent reduction in major cardiovascular events was seen. In a recent study that assessed WC, the patients with HF with both high BMI and WC had the best event-free survival.^{14,15}

Perhaps the clearest example of the profound impact of the obesity paradox is seen in patients with frailty/cachexia in HF.¹⁶ Frailty is defined as a biological syndrome characterized by declining overall function and loss of resistance to stressors, and this is known to be associated with considerable morbidity and mortality and high health care use and expenses, especially in older populations who have a high prevalence of HF. Cachexia is a particularly serious disorder of advanced HF, in which unintentional weight loss carries a greater burden of morbidity and mortality for most medical conditions, and reason exists to believe that this is the same case for advanced HF. Underweight patients often have the worst prognosis for many disorders, and this has been clearly noted in many studies describing the obesity paradox in HF.¹⁶

A limitation of most studies assessing obesity and prognosis in HF is the inability to control for nonpurposeful weight loss before study entry, which would be expected to be associated with a poor prognosis. In advanced HF, cachexia and wasting are independent predictors of higher mortality,^{16,17} and to a certain extent, overweight and obesity in HF may represent the opposite of frailty/cachexia and, therefore, may actually be an example of reverse epidemiology.¹⁸

On the other hand, although an obesity paradox exists in HF, substantial evidence also suggests that the degree or severity of obesity also substantially influences prognosis.^{1,19} The impact of morbid or class III obesity on HF prevalence and prognosis seems more concerning, particularly because recent statistics suggest that this severe obesity is increasing more so than in obesity in general.^{1,19,20} Also, the level of obesity has deleterious effects on cardiovascular structure and function and markedly increases the prevalence and severity of HF.¹⁻³ Unlike in the overweight and mild degrees of obesity, wherein an obesity paradox generally exists, studies suggest that severe or class III obesity is associated with an ominous prognosis in HF.¹⁸⁻²⁰

Evidence for Weight Loss in Heart Failure

Clinical guidelines from various societies in recent years have differed considerably regarding recommendations for weight loss. Currently none of the major societies have recommended weight loss for patients with HF who have a BMI less than 30 kg/m², with variable recommendations between the cutpoints of 30 to 40 kg/m², whereas most of the guidelines generally advocate weight loss for patients with a BMI of 40 kg/m² or greater.^{1,19,20} Because of the lack of definitive large-scale clinical trials on the role of weight loss in HF on which to base firm recommendations, the most recent HF guidelines from the American College of Cardiology Foundation/American Heart Association do not provide firm recommendations for purposeful weight loss in HF.²¹ Nevertheless, these HF guidelines recognize the poor prognosis in patients with more severe obesity, particularly those with morbid obesity. A recent study from Nagarajan and colleagues²² from the Cleveland Clinic HF program confirms the obesity paradox in 501 patients in their advanced HF clinic, but their data indicate no obesity paradox and a poor prognosis in a small group of 21 patients with morbid obesity and HF.

Therefore, based on the constellation of data, recommendations for purposeful weight loss, as opposed to nonpurposeful weight loss and cachexia (which is associated with a poor clinical prognosis), is recommended for patients with HF and more severe obesity, and this seems particularly sound for those with a BMI of 40 kg/m² or greater and seems very reasonable for most patients with HF with a BMI of 35 kg/m² or greater.^{1,16,19,20} In patients with HF and less severe degrees of obesity or those who are overweight, weight loss may be beneficial to improve symptoms and functional classification, but data on its impact on major clinical prognostic outcomes are lacking, with opposing data showing a better clinical prognosis in overweight and mildly obese patients with HF in the obesity paradox.^{1-3,20}

Hemodynamic Effects of Weight Loss

In severe obesity, substantial weight loss reduces total and central blood volume, \dot{V}_{O_2} , arterial venous oxygen differences, SV, CO, cardiac work, and LV work, with variable effects on systemic vascular resistance. Additionally, the impact of weight loss on LV filling pressures has also been variable, with reductions noted in some, but not all, patients with severe obesity.^{2,3}

Weight Loss and Cardiac Structure

Weight loss has significantly produced reductions in LV diastolic chamber size, LV wall thickness, and overall LV mass and severity of LVH.^{2,3} In a recent study, the prevalence of abnormal LV geometry (concentric remodeling or concentric or eccentric LVH) decreased from 71% to 43% with substantial weight loss.²³ Diet and exercise studies have generally demonstrated benefits of weight loss on cardiac structure, with the most dramatic effects being noted in patients who have undergone bariatric surgery and those with severe obesity.^{2,3}

Weight Loss and Diastolic Function

Studies using various noninvasive cardiac technologies have consistently demonstrated improvements in LV diastolic filling with weight loss, generally noted across the entire spectrum of obesity.¹⁻³ The reason a relative lack of concordance is seen between the weight loss-related improvements in LV diastolic filling and the sometimes lack of change in LV end-diastolic BP is not clear.^{2,3}

Effects of Weight Loss on Left Ventricular Systolic Function

Because most evidence indicates that obesity generally impacts diastolic dysfunction, as opposed to systolic dysfunction, most studies assessing LV systolic function before and after weight loss have, not surprisingly, noted impressive differences.^{2,3} In one study, LV systolic function in patients with severe obesity improved after weight reduction, but predominantly in those with baseline LV systolic dysfunction.²⁴ Recent studies using tissue Doppler and speckle track imaging before and after weight loss have demonstrated improvements in systolic mitral annular velocities and reductions in myocardial deformation in all severities of obesity, even when LV ejection phase indices were in the normal range.^{2,3,25-27} In a study by Kishi and colleagues,²⁸ increases in BMI over time, even when adjusted for other cardiovascular risk factors, were associated with adverse effects on systolic and diastolic function over 25 years, from adulthood to middle age.^{28,29}

Impact of Weight Loss on Obesity Cardiomyopathy

Whether purposeful weight loss improves mortality in patients with class I and II obesity and HF remains uncertain. Although some studies have reported a worse prognosis with weight reduction,

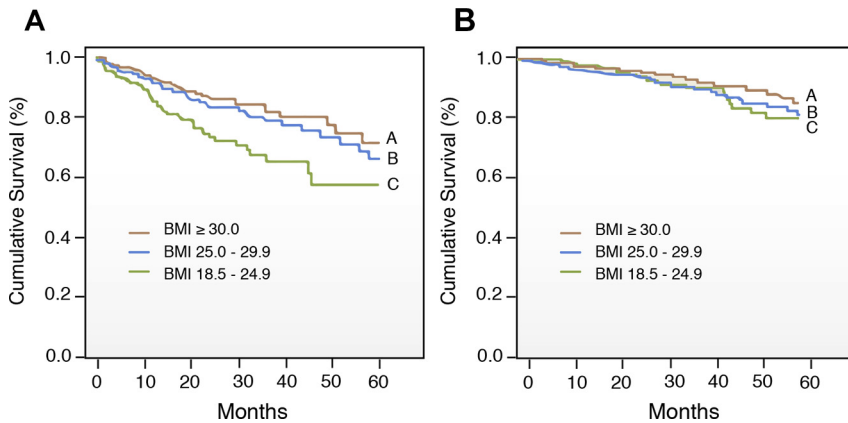


Fig. 2. Kaplan-Meier analyses according to BMI with the low CRF group (oxygen consumption <14 mL O_2 /kg/min; log rank 11.7; $P = .003$) and high CRF group (oxygen consumption ≥ 14 mL O_2 /kg/min; log rank 1.72; $P = .42$) on the left and right, respectively. (From Lavie CJ, De Schutter A, Patel DA, et al. Does fitness completely explain the obesity paradox? *Am Heart J* 2013;166:3; with permission; Adapted from Lavie CJ, Cahalin LP, Chase P, et al. Impact of cardiorespiratory fitness on the obesity paradox in patients with heart failure. *Mayo Clin Proc* 2013;88:256.)

these studies generally did not exclude patients with nonpurposeful weight loss.^{2,3,16,19} Furthermore, no large-scale studies have assessed the effects of purposeful weight loss on mortality even in patients with severe obesity. However, several small studies with dietary weight loss and bariatric surgery have noted improvements in functional class, quality of life, dyspnea, and edema after weight loss.^{2,3,10,30}

Weight Loss with Exercise Training and Improved Cardiorespiratory Fitness

A full discussion of the benefits of exercise training and improved levels of cardiorespiratory fitness (CRF) is beyond the scope of this review³¹; this is addressed elsewhere in this issue. However, one of the strongest predictors of prognosis in HF and most CVD is CRF.²⁰ In fact, even when the obesity paradox is considered, CRF remains a critical predictor of prognosis^{32,33}; HF patients with preserved CRF (defined as a peak VO_2 of ≥ 14 mL O_2 /kg/min) have a good prognosis and no obesity paradox is present.³² However, in patients with HF and low CRF (defined as peak $VO_2 < 14$ mL O_2 /kg/min) have a poor prognosis and a strong obesity paradox is present, wherein the lean patients with HF and low CRF have a particularly poor prognosis, having worse survival than overweight and, especially, obese patients with systolic HF (Fig. 2).^{32,33}

Therefore, recommendations to increase physical activity are needed throughout the health care system,³⁴ because physical activity and formal exercise training are particularly beneficial in

HF.³¹ Incorporating increasing physical activity and exercise training into a purposeful weight loss program seems to be especially attractive in efforts to reduce weight, improve symptoms and functional capacity, reduce hospitalizations, and improve survival in patients with HF.^{20,31}

SUMMARY

Large-scale clinical trials are needed to better assess and define the risks and benefits of weight loss in HF. The constellation of current data supports efforts at purposeful weight loss, particularly in those with more severe degrees of obesity, including class III obesity and many with class II obesity. Incorporating the benefits of physical activity, exercise training, and CRF into purposeful weight loss in HF seems to be a particularly attractive option for these patients.

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