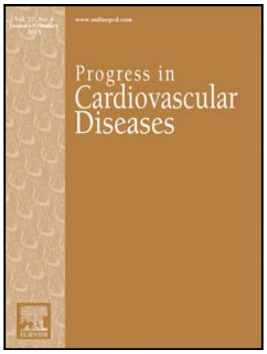

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Update on Obesity and Obesity Paradox in Heart Failure

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Abstract

Obesity has reached epidemic proportions in most of the Westernized world. Overweightness and obesity adversely impact cardiac structure and function, including on both the right and , especially, left sides of the heart, with adverse affects on systolic and, especially, diastolic ventricular function. Therefore, it is not surprising that obesity makedly increases the prevalence of heart failure (HF). Nevertheless, many studies have documented an obesity paradox in large cohorts with HF, where overweight and obese have a better prognosis, at least in the short-term, compared with lean HF patients. Although weight loss clearly improves cardiac structure and function and reduces symptoms in HF, there are no large studies on the impact of weight loss on clinical events in HF, preventing definitive guidelines on optimal body composition in patients with HF.

Abbreviations

% BF	=	Percent Body fat
BMI	=	Body mass index
BP	=	Blood pressure
CHD	=	Coronary heart disease
CO	=	Cardiac output
CRF	=	Cardiorespiratory fitness
CV	=	Cardiovascular
CVD	=	Cardiovascular disease
HF	=	Heart failure
HTN	=	Hypertension
LA	=	Left atrium or atrial
LV	=	Left ventricular
LVH	=	Left ventricular hypertrophy
LVM	=	Left ventricular mass
RV	=	Right ventricle
VO_2	=	oxygen consumption
WC	=	Waist circumference

Overweight and obesity are generally defined by body mass index (BMI) criteria, which is useful in large population studies, but flawed in individual patients, since BMI reflects both fat mass and non-fat mass (mostly muscle and skeletal mass), leading to suggestions that alternative methods to define obesity, including waist circumference (WC) , waist-to-hip-ratio, and percent body fat (% BF) may better reflect at risk body fatness. [1-3] Obesity is certainly a major risk factor for most cardiovascular (CV) diseases (CVD), including for hypertension (HTN) and coronary heart disease (CHD), two of the major risk factors for the development of heart failure (HF).[1,4-6] Additionally, obesity has more direct effects on the pathogenesis of HF, due to its negative impact on cardiac morphology and performance, including negative impact on both systolic and, especially, diastolic left ventricular (LV) function.[5,6,7,8] Therefore, it is of no surprise that HF is dramatically increased in the setting of obesity.

However, despite the adverse effects that obesity has on CVD risk factors and its association with increased incidence of most CVD, including HTN and CHD, (both of which are strongly related with the increased risk of HF), and for HF itself, many large studies have demonstrated the powerful "obesity paradox" in cohorts with established HF. In fact, the presence of overweight and obese , at least mild obesity in those with HF , appears to confer a better short- and intermediate-term prognosis than in their leaner counterparts who have similar degrees of HF.[5,6,9]

In this review, we describe the adverse effects of overweight/obesity on hemodynamics, as well as on cardiac structure and ventricular function. The impact of obesity on HF prevalence is reviewed, as well as studies showing an obesity paradox in HF. Finally, we discuss the role of fitness and weight loss in obese patients with HF, as well as the need for more studies on this topic.

Impact of Obesity on Cardiac Morphology and Performance

Alpert and colleagues[7,8] have recently reviewed this topic in detail. Considerable evidence underscores the adverse effects of excessive adipose accumulation and associated fat-free mass on central and peripheral hemodynamics, as well as on cardiac structure and systolic and diastolic LV function (Figure 1, Table 1).[5,7]

<u>Hemodynamics</u>. There are many hemodynamic alterations in obesity, leading to increased total and central blood volume and increased stroke volume and cardiac output (CO).[5,7,8] Typically, obesity leads to a reduction in systemic vascular resistance in normotensive obese persons, which facilitates the increase in CO despite the fact that heart rate is not substantially impacted in obesity. Arteriovenous oxygen differences are usually widened in obesity, due to lower oxygen extraction by adipose tissue. Thus, blood flow per unit of weight is reduced, especially in more severe degrees of obesity and in combined obesity/HTN, where systemic vascular resistance is also increased.[5,7,8]

In Class II and III obesity, increased venous return leads to increased preload with increased LV filling pressure. This further contributes to elevated pulmonary artery and right heart pressures.[5,7,8] With exercise in Class III obesity, central blood volume increased by 20%, LV end-diastolic pressure increased by 50%, and the LV dP/dt increased by 57%.[5,10]

<u>Cardiac Structure</u>. Obesity also produces marked abnormalities in cardiac structure, including LV hypertrophy (LVH),[5,7,8,11] as well as enlargement of the atria and right side of the heart. Although LV mass (LVM) is commonly increased in obesity,[5,7,8,11,12] blood pressure (BP) seems to be an important component of such augmentation. Additionally, LVM markedly increases progressively with the severity of obesity. Based on the hemodynamic alterations discussed previously, it seems logical that the elevated blood volume and CO would lead to LV dilatation and more eccentric LVH. However, several studies suggest that in Class I and II obesity, the incidence of concentric remodeling and concentric LVH may exceed the incidence of eccentric LVH.[5.7,8] However, without elevated BP, eccentric LVH may be more prevalent. Obviously, studies that assess the impact of obesity on LV geometry should account for obesity severity and levels of BP, as well as duration of obesity.[5,7,8]

Ventricular Function. Obesity also has adverse effects on ventricular function.[5,7,8,11,12] Most studies assessing LV systolic function in obese patients using LV ejection phase indices have reported normal or even hyperdynamic LV function. Even in severe obesity, LV systolic dysfunction is relatively uncommon in the absence of coexisting CVD. In severe obesity, however, the presence of severe LVH causes blunting of the exercise induced rise in LV systolic function. Additionally, studies using tissue Doppler imaging have reported subclinical LV systolic dysfunction in obesity that is thought to be load independent, suggesting the presence of intrinsic abnormalities of LV contraction.[5,7,8,11,12]

More importantly, however, studies demonstrate impaired LV diastolic function in obese patients, especially in combination with LVH.[5,7,8] Nevertheless, some studies have reported diastolic LV dysfunction independent of LVM. Although LV diastolic dysfunction has been reported for many years with several imaging techniques,[5,7,8,12,13] more recent studies with tissue Doppler have particularly identified LV diastolic dysfunction as a subclinical disorder in obesity. The prevalence of LV diastolic dysfunction increases with increases of severity of obesity, from 12% of Class I, 35 % of Class II, and 45 % of Class III obese patients in one study. [14] Most studies demonstrating impaired LV diastolic function in obesity have reported a high prevalence of LVH, with progressive impairment of LV diastolic function with increasing LVM (presumably due to muscle, fibrosis and intra-myocardial fat.) [5,7.8]

Additionally, obesity has adverse affects on the left atrium (LA) and right ventricle (RV), and particularly abnormalities are noted with the common combination of obesity, HTN, and LVH.[5,7,8,12,13,15]Recent studies have reported abnormal LA strain in obesity, particularly in those with more LA enlargement and coexisting HTN. [7,16] RV function has not been as extensively studied in obesity, partly due to difficulties with older imaging techniques in obese patients, but studies employing tissue Doppler imaging show reduced systolic and diastolic velocities of the lateral tricuspid valve annulus and reduced RV strain.[7]

Obesity and HF

Considering the adverse effects of adiposity on hemodynamics and LV structure and ventricular function, not surprisingly, obesity leads to marked increases in the prevalence of HF.[5,6] Additionally, myocardial lipotoxicity and lipoapoptosis has also been described with severe obesity in animal models and may potentially contribute to an obesity cardiomyopathy in humans; however, other factors, including increased activation of the renin-angiotensin-aldosterone system, increased sympathetic tone, insulin resistance, and hyperleptinemia are likely much more important .[7, 8] Although a detailed discussion of the pathophysiology related with leptin in the development of CVD and HF is beyond the scope of this review and is briefly reviewed elsewhere, [1] leptin is involved with increasing BP and the development of HTN, as well as leading to vascular and myocardial injury, that may be important in the pathogenesis of HF.

The largest study to assess the risk of HF in obesity is derived from the Framingham Heart Study.[17] In a study of 5,881 participants, Kenchaiah and colleagues[17] demonstrated a marked increase in the prevalence of HF in both men and women. In fact, for every 1 kg/m^2 increase in BMI, the risk of HF increased by 7% in women and 5% in men, with graded increases in HF prevalence across all BMI categories (Figure 2).[17] Alpert and colleagues[18] have reported that HF is also strongly impacted by obesity severity and duration of obesity. In a study of 74 morbidly obese patients, nearly ⅓ had clinical evidence of HF, and the probability of HF increased substantially with increasing duration of morbid obesity, with prevalence rates exceeding 70% at 20 years and 90% at 30 years.[18]

Obesity Paradox in HF

Despite the adverse affects of obesity on LV structure and function that markedly increases the prevalence of HF in obesity, numerous studies have now reported a powerful relationship between obesity and prognosis, with overweight and, especially, obese Class I and II HF patients having the better prognosis than do their leaner counterparts with HF.[5,6] Horwich and colleagues[19] first described this almost 15 yeas ago, and this association has now been confirmed in many studies and meta-analyses. Sharma and colleagues[20] recently reported a meta-analysis of 6 studies (N=22,807) that assessed adverse events, including CV mortality, all-cause mortality, and rehospitalizations, during a 2.9 year mean follow-up (Figure 3);[20] prognosis was the worst with low BMI, whereas the lowest risk occurred in the overweight Another study of 6,142 patients with acutely decompensated HF from 12 prospective studies from 4 continents also confirmed an obesity paradox, mostly confined to older persons, those with reduced cardiac function, less cardiometabolic illness, and recent onset HF.[21] A study from the Cleveland Clinic of 3,811 patients with systolic HF showed that the survival paradox of high BMI disappeared in males after adjustments for potential confounders(age, race, HF etiology, New

York Heart Association classification, drug therapy, and exercise performance), with overweight and obese males showing higher adjusted mortality hazard ratios compared to normal weight males.[9,22] On the other hand, overweight female patients had a significant 16% lower mortality with a nadir in mortality hazard just below the cutpoint of 30 kg/m^2. The multivariate model also supported a differential impact of BMI on mortality in males vs. females. Although other studies have indicated an obesity paradox in HF independent of gender,[9] this recent analysis had substantial information on potential confounders that were not present in at least some of the other studies.

Additionally, most of the studies assessing the obesity paradox in HF have only used BMI and not measured other variables of body composition and obesity, such as % BF or WC. However in a study of 209 patients with advanced systolic HF, Lavie et al[23] demonstrated an obesity paradox with both BMI and % BF. In fact, for every 1% increase in % BF, there was a 13% independent reduction in major CV events. A recent study from Clark et al[24,25] demonstrated that both higher BMI and higher WC were associated with better event-free survival in HF, with the best survival being noted in those with both high BMI and high WC.[6,24,25]

Mechanisms for the Obesity Paradox in HF

The mechanisms for the obesity paradox in CVD and HF particularly remain somewhat unclear and difficult to reconcile, but several potential reasons are listed in Table 2.[5] Certainly, advanced HF is a catabolic state, and heavier HF patients may have more metabolic reserve, whereas frail and cachectic patients (discussed later) experience greater morbidity and mortality for many diseases, including HF. Adipose tissue is also known to promote soluble tumor necrosis factor-alpha receptors that could be protective in patients with greater adiposity by neutralizing tumor necrosis factor. Additionally, overweight and obese HF patients have reduced expression of circulating natriuretic peptides,[5,26] which could lead obese HF patients to become symptomatic with edema and dyspnea and present earlier with excess volume accumulation occurring at less severe stages of HF, which could lead to earlier treatment with cardioprotective medications. Because obesity is usually associated with greater blood volume and BP, obese patients with HF should be able to tolerate higher doses of various cardioprotective CV medications. Also, although most studies adjust for age, generally the obese HF are slightly younger than the leaner patients, as noted in the 4 year younger age in our recent meta-analysis.[20] As discussed below, adipose tissue in HF may be associated with greater muscular strength, that along with cardiorespiratory fitness (CRF) could also improve HF prognosis.[27,28]

Impact of Frailty/Cachexia in HF

Frailty can be defined as a biological syndrome that is characterized by declining overall function and loss of resistance to stressors, which is associated with increased morbidity, mortality, and healthcare expenditures, particularly in the elderly, who have a high prevalence of HF.[28] A recent study indicates that frailty was highly prevalent among community patients with HF, and this predicted a significant increase in the risk of hospitalization and emergency department encounters, independent of other comorbidities.[29]

Cachexia is a particularly ominous accompaniment of advanced HF.[28] Certainly, unintentional weight loss carries an extremely high burden of morbidity and mortality for most medical conditions, and the same is true for HF. Although many studies have suggested a worse prognosis associated with weight loss in HF, a limitation of most of these studies is that purposeful weight loss was not differentiated from non-purposeful weight loss, and studies generally were not able to account for nonpurposeful weight loss prior to study entry.[5,28] To an extent, overweight and obesity in HF may represent the opposite of cachexia, or reverse epidemiology.[28,30]

Recent studies have suggested that fat loss may precede lean muscle mass loss as cardiac cachexia becomes manifest, and fat loss may signal the onset of declining prognosis in HF.[28,31] These studies have also made a link between cardiac cachexia and RV dysfunction. Besides preventing weight loss, potentially useful strategies for cardiac cachexia in HF are discussed elsewhere.[28]

Impact of Severe or Class III Obesity

Although an obesity paradox exists for most CVD as well as HF, it is most likely that this mostly applies to overweight and mildly obese patients, less so for Class II obesity (BMI 35-40 kg/m^2) and probably not for more severe, or Class III obesity (BMI ≥ 40 kg/m^2).[32,33] In CHD, for example, although an obesity paradox was noted short-term for all classes of BMI, more severe obesity was associated with worse survival during long-term follow-up.[34,35] The impact of morbid or Class III obesity in HF prevalence and prognosis is most concerning, since recent studies suggest that more severe obesity is increasing more so than obesity per se.[1,5] Additionally, this level of severe obesity has particularly detrimental affects on CV structure and function, and, as discussed previously, markedly increases the prevalence of HF.[5,7,18] Unlike less severe degrees of obesity, where an obesity paradox generally seems to exist, at least in short-term follow-up studies, many studies suggest that Class III obesity is associated with a poor HF prognosis.[32,33]

Impact of Fitness in HF

Substantial data indicate that muscular strength and levels of CRF markedly impacts prognosis in many CVD patients, including HF.[27,36] In fact, low levels of CRF may be one of the strongest risk factors for CVD and total mortality.[37-39] High levels of CRF, including higher workloads on treadmill stress tests, longer 6-minute walking time, and higher peak oxygen consumption (VO_2) , are associated with better prognosis in most CVD, including CHD and HF.[36-41] In addition, Lavie and colleagues[42] demonstrated that CRF strongly mitigates the impact of adiposity on subsequent prognosis in HF. In a study of 2,066 patients with systolic HF, those with a relatively preserved CRF (peak $VO_2 \geq 14$ cc/kg/min) have a favorable prognosis regardless of weight. In contrast, those with poor CRF (peak $VO_2 < 14$ cc/kg/min), a strong obesity paradox was apparent (Figure 4), with the lean HF patients, even after excluding underweight patients, with poor CRF having particularly high mortality compared with heavier patients.[42] These data were recently confirmed in a study from Clark et al.[43]

These data support physical activity and exercise training to increase levels of CRF to improve prognosis in HF patients.[36] Although the results of the recent HF: ACTION (Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training) were less impressive than expected, as the exercise training only produced a modest 4% average increase in peak VO_2,(which was well less than the 10% to 15% improvements anticipated),[44] still this therapy reduced the primary endpoint of all-cause mortality in HF hospitalizations by 11% after adjusting for baseline factors. However, in patients who were more compliant with exercise training, greater increases in peak VO_2 were associated with 30% reductions in mortality and hospitalizations.[45] Therefore, recommending exercise training to improve CRF is important to improve HF prognosis. Although randomized controlled trials of resistance training on long-term prognosis are not available in HF, many studies have demonstrated better prognosis associated with higher levels of muscular strength, which are also associated with better quality of life.[27,28] Thus, it is reasonable based on current information to include resistance training with aerobic exercise training for most patients with HF.

Intentional Weight Loss in HF

Intentional weight loss may be one of the most effective long-term therapies for improving the hemodynamics and cardiac structure and functional abnormalities associated with obesity, most of which adversely impact HF.[5,7] Despite this evidence, however, and considering the previously discussed obesity paradox and adverse impact of cardiac cachexia and frailty in HF,[5,7,28] the major HF societies during the past decade have vastly different recommendations regarding intentional weight loss strategies, with none recommending weight loss for the overweight BMI patients.[5] Because of the lack of definitive large-scale clinical trials on the role of weight loss in HF to make firm guidelines and recommendations, the more recent HF guidelines from the American College of Cardiology Foundation/American Heart Association do not provide any firm recommendations for intentional weight loss in HF, except for the recognition of the particularly poor prognosis present in severe or morbid, Class III obesity (BMI ≥ 40 kg/m^2).[46]

Therefore, based on the constellation of data, recommendations for purposeful weight loss, including possibly bariatric surgery, for severely obese HF patients, seem sound, and this seems reasonable for moderate-severe obesity, with BMI ≥ 35 kg/m^2.[5,7,9] In less severe obesity and in overweight HF patients, although weight loss may improve symptoms and functional class, data on major HF morbidity and mortality are lacking. Therefore, in overweight and mildly obese HF patients, prevention of weight gain and improving CRF may be preferable goals.[36,47-49]

Conclusions

Obesity adversely affects hemodynamics and cardiac structure and function, leading to systolic and, particularly diastolic LV dysfunction. Despite this effect, however, many studies suggest an obesity paradox, where overweight and mildly obese HF patients have a better prognosis than do normal weight patients with HF. In contrast, underweight HF patients, as well as those with frailty and cardiac cachexia, particularly have a poor prognosis. Although long-term studies of intentional weight loss in HF are generally lacking, the constellation of data support intentional weight loss for high risk patients with more severe obesity, whereas effects to improve levels of CRF and muscular strength are preferable in most HF patients.

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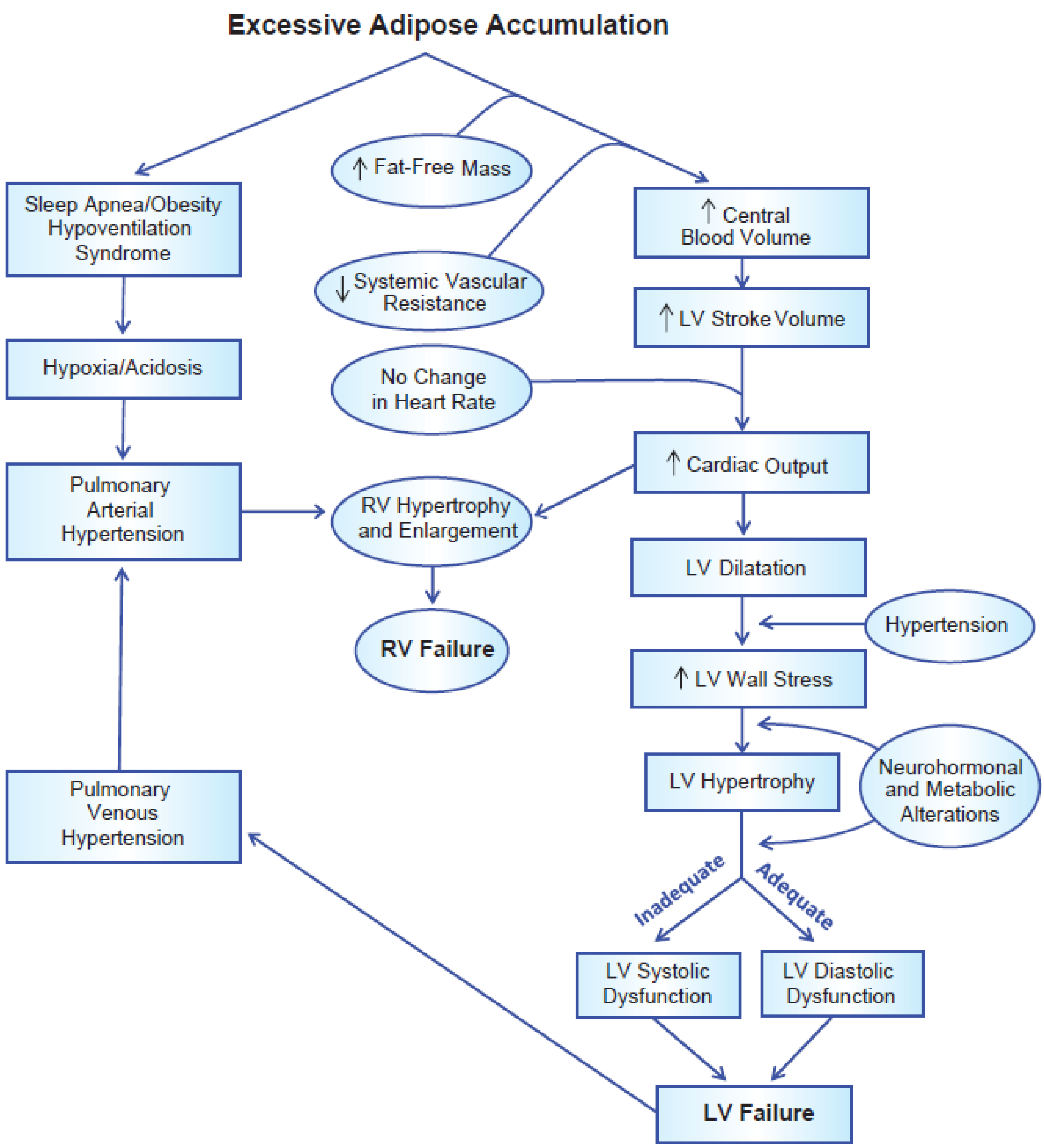
Figure Legends

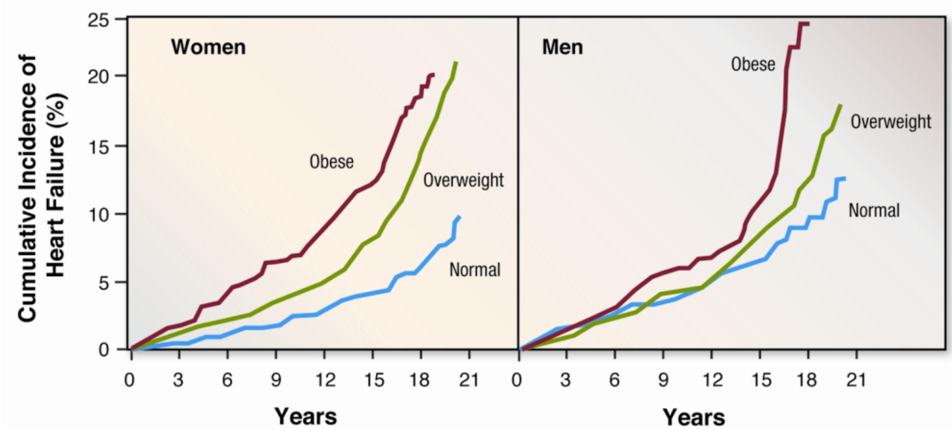
1. Proposed pathophysiology of obesity cardiomyopathy. This diagram shows the central hemodynamic alterations that result from excessive adipose accumulation in severely-obese patients and their subsequent effects on cardiac morphology and ventricular function. Left ventricular (LV) hypertrophy in severe obesity may be eccentric or concentric. Factors influencing LV remodeling and geometry include severity and duration of obesity, duration and severity of adverse LV loading conditions (particularly hypertension) and possibly, neurohormonal and metabolic abnormalities such as increased sympathetic nervous system tone, activation of the renin–angiotensin–aldosterone system, insulin resistance with hyperinsulinemia, leptin resistance with hyperleptinemia, adiponectin deficiency, lipotoxicity and lipoapoptosis. These alterations may contribute to the development of LV failure. LV failure, facilitated by pulmonary arterial hypertension from sleep apnea/obesity hypoventilation may subsequently lead to right ventricular failure. Reproduced with permission from Alpert MA et al.[7]
2. *Risk of Heart Failure*. Prevalence of heart failure in 5,881 Framingham participants according to obesity status. Reproduced with permission from Kenchaiah et al.[17]
3. Meta-analysis of six studies (n-22,807) on impact of body mass index on cardiovascular mortality, all-cause mortality, and hospitalizations in heart failure. Reproduced with permission from Sharma et al.[20]
4. Kaplan-Meier analyses according to body mass index (BMI) with the low cardiorespiratory fitness (CRF) group (O_2 consumption < 14 $mLO_2\,kg^{-1}\,min^{-1}$, log rank 11.7, P=.003) and high CRF group (O_2 consumption ≥ 14 $mLO_2\,kg^{-1}\,min^{-1}$, log rank 1.72, P=.42) on the left and right,

respectively. Reproduced with permission from Lavie et al[49] and adapted from data published in Lavie et al[42].



Excessive Adipose Accumulation
Sleep Apnea/Obesity Hypoventilation Syndrome
↑ Fat-Free Mass
↑ Central Blood Volume
↓ Systemic Vascular Resistance
↑ LV Stroke Volume
Hypoxia/Acidosis
No Change in Heart Rate
↑ Cardiac Output
Pulmonary Arterial Hypertension
RV Hypertrophy and Enlargement
LV Dilatation
RV Failure
Hypertension
↑ LV Wall Stress
LV Hypertrophy
Neurohormonal and Metabolic Alterations
Pulmonary Venous Hypertension
Inadequate
Adequate
LV Systolic Dysfunction
LV Diastolic Dysfunction
LV Failure

Figure 1



No. at Risk:

Normal	1729	1688	1634	1568	1477	1227	295	869	822	758	690	637	512	105
Overweight	955	929	880	815	757	634	248	1378	1322	1254	1163	1071	971	171
Obese	493	477	448	409	372	296	104	457	433	403	370	342	276	51

Figure 2

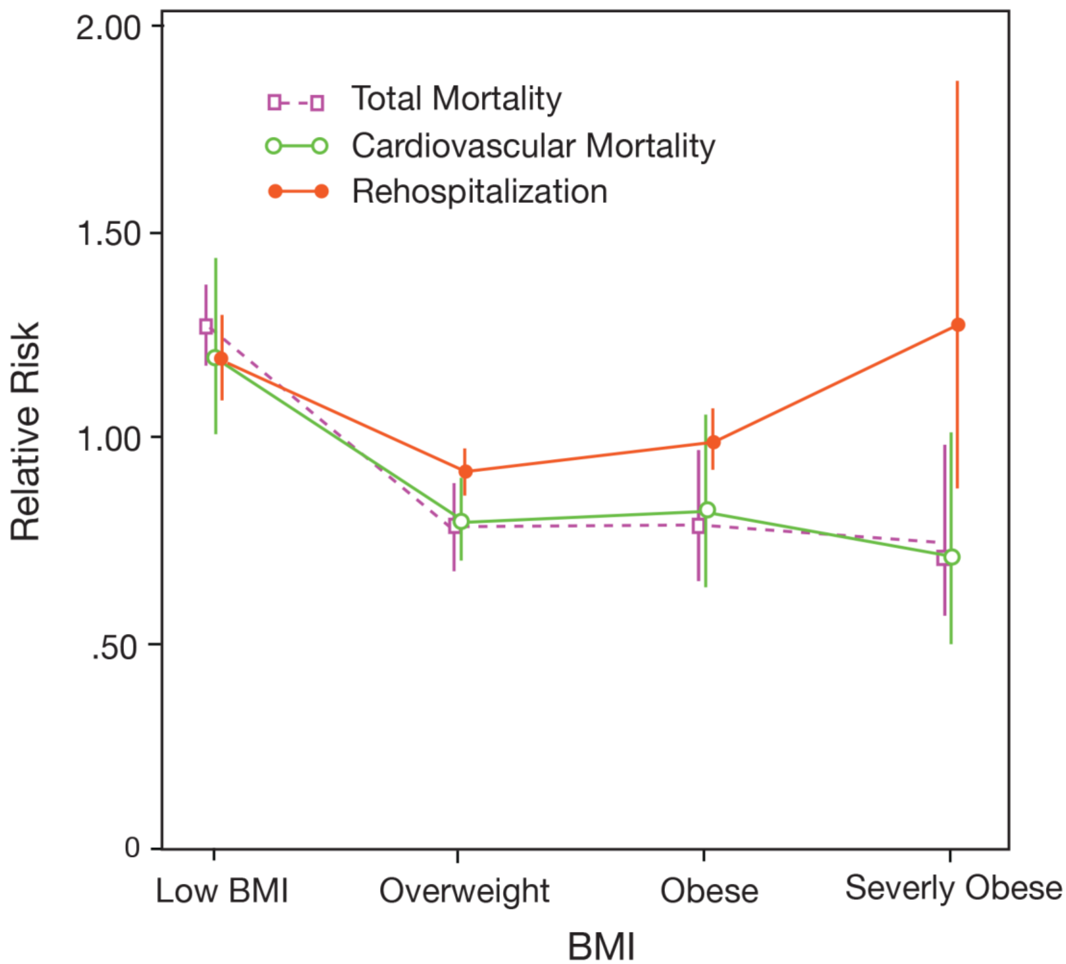

2.00
1.50
1.00
.50
0
Relative Risk
Total Mortality
Cardiovascular Mortality
Rehospitalization
Low BMI
Overweight
Obese
Severly Obese
BMI

Figure 3

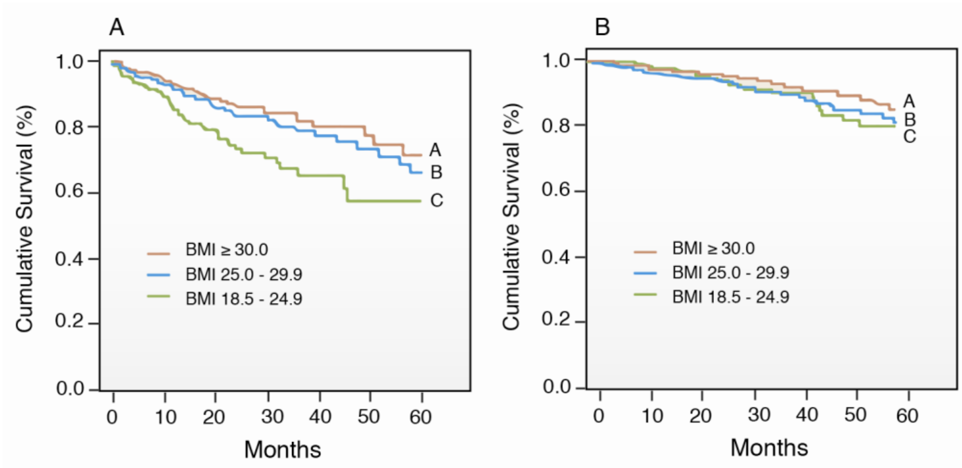

A
1.0
0.8
0.6
0.4
0.2
0.0
Cumulative Survival (%)
0
10
20
30
40
50
60
Months
A
B
C
BMI ≥ 30.0
BMI 25.0 - 29.9
BMI 18.5 - 24.9
B
1.0
0.8
0.6
0.4
0.2
0.0
Cumulative Survival (%)
0
10
20
30
40
50
60
Months
A
B
C
BMI ≥ 30.0
BMI 25.0 - 29.9
BMI 18.5 - 24.9

Figure 4

Table 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. Over-expression 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

LV = left ventricular; RV = right ventricular

Table 2. Potential Reasons for the Obesity Paradox in HF

1. Nonpurposeful weight loss.
2. Greater metabolic reserves
3. Less cachexia
4. Protective cytokines
5. Earlier presentation[a]
6. Attenuated response to renin-angiotensin-aldosterone system
7. Higher blood pressure leading to more cardiac medications
8. Different cause of HF
9. Increase muscle mass and muscular strength
10. Implications related to cardiorespiratory fitness

[a]Caused by lower atrial natriuretic peptide levels, restrictive lung disease, venous insufficiency, and so on.

Reproduced with permission from Lavie CJ et al.[5]