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STATE-OF-THE-ART PAPER

Impact of Obesity and the Obesity Paradox on Prevalence and Prognosis in Heart Failure

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Obesity has reached epidemic proportions in the United States and worldwide. Considering the adverse effects of obesity on left ventricular (LV) structure, diastolic and systolic function, and other risk factors for heart failure (HF), including hypertension and coronary heart disease, HF incidence and prevalence, not surprisingly, is markedly increased in obese patients. Nevertheless, as with most other cardiovascular diseases, numerous studies have documented an obesity paradox, in which overweight and obese patients, defined by body mass index, percent body fat, or central obesity, demonstrate a better prognosis compared with lean or underweight HF patients. This review will describe the data on obesity in the context of cardiopulmonary exercise testing in HF. Additionally, the implications of obesity on LV assist devices and heart transplantation are reviewed. Finally, despite the obesity paradox, we address the current state of weight reduction in HF. (J Am Coll Cardiol HF 2013;1:93–102)

There are numerous adverse effects of overweightness and obesity, usually defined by body mass index (BMI) criteria, on general and, particularly, cardiovascular (CV) health. Obesity has been implicated as 1 of the major risk factors for hypertension (HTN) and coronary heart disease (CHD), both of which are strongly related to the development of heart failure (HF), and may be an independent predictor of the development of HF via adverse effects on cardiac structure and left ventricular (LV) systolic and, especially, diastolic function (1). However, despite the known strong association between overweight/obesity and CV risk factors and the development of CV diseases, numerous studies, including in HF, have demonstrated an "obesity paradox," in that obese patients with established CV diseases appear to have a more favorable clinical prognosis than do their leaner counterparts with the same CV diseases (1).

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This paper describes the hemodynamic alterations of overweight/obesity and its pathological effects on arterial blood pressure (BP) and cardiac structure and function, thus contributing to its role in HTN and CHD, as well as HF. We also address the impact of obesity in the increasing incidence and prevalence of HF, as well as the evidence for an obesity paradox in overweight/obese patients with established HF. Additionally, we describe the influence of obesity on the assessment of prognosis in HF, including the use of cardiopulmonary exercise testing (CPX), the impact of obesity on various advanced therapies for HF, including heart transplantation (HT) and left ventricular assist devices (LVADs), as well as the potential role of intentional weight reduction in the prevention and treatment of HF.

Impact of Obesity on Hemodynamics and Left Ventricular Structure and Function

Considerable evidence demonstrates the adverse effects of obesity on central and peripheral hemodynamics, as well as on cardiac structure and function (Fig. 1, Table 1). Total blood volume and cardiac output correlate positively and proportionately with the degree of excess body weight (2,3). Fat-free (non-osseous) mass is thought to contribute to these alterations as augmentation of total blood volume, and cardiac output cannot be accounted for by excess fat mass alone. The increase in cardiac output and cardiac work are attributable to a rise in LV stroke volume and stroke work, because heart rate does not differ from that predicted for ideal body weight (2,3). In class II (BMI 35 to 39.9 kg/m^2) and

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Abbreviations and Acronyms

BMI = body mass index
BP = blood pressure
CHD = coronary heart disease
CPX = cardiopulmonary exercise testing
CV = cardiovascular
HF = heart failure
HT = heart transplantation
HTN = hypertension
LV = left ventricular
LVAD = left ventricular assist device
LVH = left ventricular hypertrophy
MCS = mechanical circulatory support
O_2 = oxygen
RAAS = renin-angiotensin-aldosterone system
RV = right ventricular
VE/VCo_2 = minute ventilation/carbon dioxide production
Vo_2 = oxygen consumption

III (BMI $\geq$40.0 kg/m^2) obese patients, oxygen (O_2) consumption (Vo_2), arteriovenous O_2 difference, cardiac output, stroke volume, right ventricular (RV) end-diastolic pressure, mean pulmonary artery pressure, pulmonary vascular resistance, and mean arterial pressure exceed those predicted for normal weight patients (2,4). Systemic vascular resistance in obese patients is typically low in normotensive patients and either normal or elevated, but lower than expected, in hypertensive obese patients (1,2–5). With exercise in class III obese patients, central blood volume increases by 20%, LV end-diastolic pressure increases by 50% (from an already elevated 21 to 31 mm Hg), and LV dP/dt increases 57% (4).

In autopsy studies of class III obesity, all subjects had increased heart weight, LV wall thickness, and microscopic LV hypertrophy (LVH) with a variable prevalence of increased RV wall thickness and excess epicardial fat (6,7). Unfortunately, none of these autopsy studies excluded patients with HTN or CHD, so this might not be representative of uncomplicated class III obesity. Subsequent echocardiographic studies of normotensive class III obese subjects identified LV enlargement in 40%, increased LV wall thickness in 56%, increased LV mass in 64%, left atrial enlargement in 50%, and RV enlargement in 33% of patients studied (7,8). In a study of 3,922 patients from the Framingham study, Lauer et al. (9) found that BMI correlated positively with LV wall thickness, LV internal dimension in diastole, and LV mass, even after adjusting for age and BP, particularly in those whose BMI was >30 kg/m^2 (2,9). Kasper et al. (5) studied 409 lean patients and 43 patients whose BMI was $\geq$35 kg/m^2, and HF was present in all patients. In this study, there was a higher prevalence of dilated cardiomyopathy in obese patients compared with lean patients. A specific cause for dilated cardiomyopathy was identified in 64% of lean patients but in only 23% of obese patients, suggesting the obese state was a contributing factor to the etiopathogenesis. Myocyte hypertrophy was detected in 67% of biopsies of obese patients, which not only lent credence to the concept of a cardiomyopathy of obesity, but also confirmed that LVH is a key component of this disorder (5). Multiple echocardiographic studies compared LV morphology in lean and obese patients (7–10). The degree of obesity in these studies varied from stage I to stage III (7–10). Virtually all of these studies demonstrated that the LV internal dimension (or volume) in diastole, LV wall thickness, and LV mass or mass index were significantly greater in obese patients than in lean patients (7,8,10). Studies of normotensive class III obese patients indicated that systolic BP, LV end-systolic wall stress, and LV chamber size in diastole (surrogates for afterload and preload) were responsible in part for these morphologic alterations (7,8,10), and duration of obesity also appeared to be an important factor in their development (11,12). Originally, the presence of LVH in obese patients was attributed to increased adipose tissue. However, more recent information suggested that fat-free mass was an independent and stronger predictor of LV mass than fat mass in class I and II obesity (13). Whether this relationship holds for class III obesity in uncertain. It stands to reason that the development of LVH in obesity would predispose a patient to LV diastolic dysfunction. Hemodynamic studies, particularly in class III obese patients, commonly reported elevated LV end-diastolic pressure (2,3,5). In 1 study, Doppler echocardiographic indexes of diastolic function showed that LV diastolic dysfunction occurred in 12% of class I, 35% of class II, and 45% of class III obese patients (14). Multiple studies using various echocardiographic and radionuclide techniques to assess diastolic function in lean and class I, II, and III obese subjects confirmed these diastolic filling abnormalities in obesity, particularly in those with LVH (14–18). Adverse LV loading conditions and duration of obesity appeared to contribute to this phenomenon (12,15,16). However, recent studies that used tissue Doppler imaging of the mitral annulus indicated that peak myocardial velocity in diastole declined as obesity severity increased, suggesting a load-independent mechanism for LV diastolic dysfunction in obesity (18).

Most studies that compared lean and obese patients with variable degrees of severity of obesity showed no significant differences in LV ejection phase indexes between lean and obese subjects (2,19). In those studies that showed lower LV systolic function in obese subjects than in lean subjects, the differences were small, and LV ejection phase indexes remained within the normal range in most instances (2,19). Even in stage III obese patients, severe LV systolic dysfunction was uncommon in the absence of coexistent CV disease (2,19). As with LV mass and LV diastolic filling, adverse loading conditions and duration of obesity might also contribute to the relatively uncommon LV systolic dysfunction in obesity (20). Recent studies that employed tissue Doppler imaging of the mitral annulus indicated a progressive decline in peak myocardial velocity in systole with increasing severity of obesity. Abnormal myocardial strain and strain rate were also detected in obese subjects using tissue Doppler imaging techniques. These alterations suggested the presence of a load-independent mechanism for subclinical LV systolic dysfunction in obesity (18). In class III obese patients, the change in LV ejection fraction with exercise was blunted in those with LVH (2,19,21).

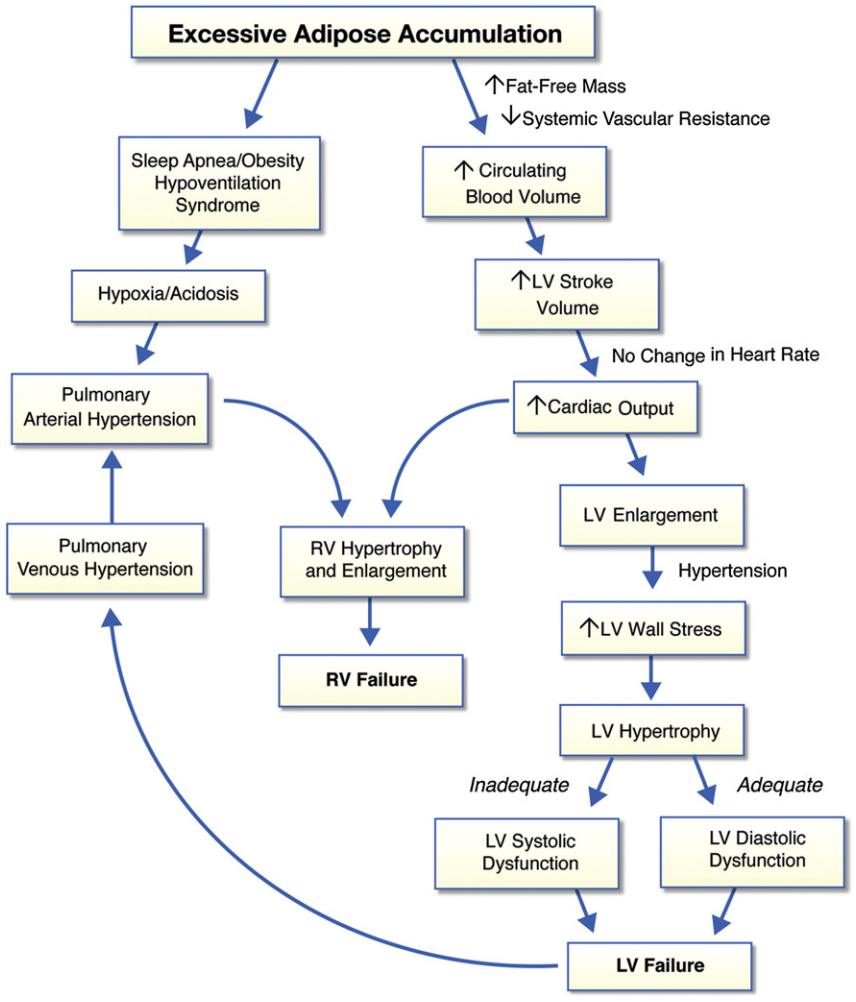

Figure 1 **Pathophysiology of Obesity Cardiomyopathy**

This shows the central hemodynamic, cardiac structural abnormalities, and alterations in ventricular function that may occur in severely obese patients and predispose them to heart failure. Left ventricular (LV) hypertrophy in severe obesity may be eccentric or concentric. In uncomplicated (normotensive) severe obesity, eccentric LV hypertrophy predominates. In severely obese patients 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.

Based largely on the aforementioned studies, a pathophysiological mechanism can be developed to describe the pathophysiological alterations in uncomplicated obesity that may lead to HF (2,3,7–10,12–21), which is most applicable to class III obesity, but in principle may apply in part to those who are less severely obese. These alterations are shown in Figure 1.

HTN occurs in close to 50% of obese patients and more so in class III obesity (2). Compared with normotensive obese patients, hypertensive obese patients have lower total and central blood volume and higher LV stroke volume and cardiac output (22,23). Systemic vascular resistance is higher in hypertensive obese patients than in normotensive obese patients and has been characterized as "inappropriately normal" by some investigators (22,23). The effect of coexistent HTN and obesity on LV morphology depends largely on the relative severity and duration of both disorders; HTN alone promotes the development of concentric LVH or concentric remodeling, whereas when long-standing HTN is combined with chronic severe obesity, a hybrid form of LVH develops (2,19,22,23). Previously characterized as eccentric-concentric LVH, this morphology is now characterized as a form of concentric LVH. It is important to understand that the relative severity and duration of obesity and HTN may dictate the specific LV geometric profile in hypertensive obese patients.

Older studies suggested that uncomplicated obesity predisposes to eccentric LVH (2,7,8,19); however, recent

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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. 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

LV = left ventricular; RV = right ventricular.

studies challenged this concept by reporting an incidence of concentric LV remodeling and LVH that equalled or exceeded that of eccentric LVH (although some adjusted for HTN, most included HTN) (24). Although concentric LVH and LV remodeling clearly occur to a variable extent in obese patients, most studies in obese normotensives showed a predominance of eccentric LVH (2,7,19). Potential reasons for concentric remodeling or concentric LVH in obese patients include failure to adjust for HTN or consider the relative severity and duration of HTN and obesity, underdiagnosis of HTN, sympathetic nervous system and renin-angiotensin-aldosterone system (RAAS) activation, the effects of growth factors (e.g., insulin-like growth factor), and reclassification of eccentric-concentric LVH as concentric LVH (2,19).

A variety of metabolic abnormalities have been identified in animal models of obesity that contribute to the development of LV systolic and diastolic dysfunction and/or to LVH. These include lipotoxicity and lipoapoptosis, insulin resistance with hyperinsulinemia, leptin resistance and hyperleptinemia, reduced adiponectin levels, activation of the sympathetic nervous system, and activation of the RAAS. Whether and to what extent these metabolic abnormalities contribute to alterations in cardiac structure and function in normotensive humans is uncertain.

Obesity and HF

In a study of 5,881 Framingham Heart Study participants, Kenchaiah et al. (25) demonstrated that for every 1 kg/m^2 increase in BMI, the risk of HF during a 14-year follow-up increased by 5% in men and 7% in women, with graded increases in the risk of HF noted across all BMI categories (Fig. 2) (25). However, in a study of 550 subjects without diabetes in Greece, BMI was not associated with HF risk, whereas metabolic syndrome was associated with a 2.5-fold higher HF risk (26). In contrast to normal weight patients with metabolic syndrome, metabolically healthy obese subjects had a decreased HF risk in a 6-year follow-up study. In a study by Alpert et al. (10) of 74 morbidly obese patients, nearly one-third had clinical evidence of HF, and the probability of HF increased dramatically with increasing duration of morbid obesity, with prevalence rates exceeding 70% at 20 years and 90% at 30 years.

Obesity Paradox and HF

Despite the adverse effects of obesity on LV structure and function, including adverse effects on both systolic and, especially, LV diastolic function, as well as the epidemiological data showing a powerful relationship between obesity, generally defined by BMI criteria, and HF prevalence, numerous studies have suggested that obese patients with HF have a better prognosis than do their leaner counterparts (1). One of the first studies to demonstrate the obesity paradox in HF was by Horwich et al. (27), who demonstrated that the best HF prognosis occurred in overweight patients, followed closely by obese patients, and the worst prognosis occurred in underweight HF patients, followed closely by patients with "normal" BMI (Fig. 3). Lavie et al. (28) previously expanded on this observation by demonstrating that the relationship between improved survival and poorer body habitus was also present by measurement of percent body fat (Fig. 4) (28). In a study of 209 patients with advanced chronic systolic HF, Lavie et al. (28) demonstrated that for every 1% increase in percent body fat, there was a 13% independent reduction in major CV events (27). A recent study demonstrated that both higher BMI and higher waist circumference were associated with better event-free survival in HF (29).

In a meta-analysis of 9 observational HF studies (n = 28,209) in which patients were followed for an average of 2.7 years, Oreopoulous et al. (30) demonstrated that compared with patients with normal BMI, overweight and obese HF patients had reductions in CV (−19% and −40%, respectively) and all-cause (−16% and −33%, respectively) mortality. In an analysis of in-hospital mortality in >100,000 decompensated HF patients, higher BMI was associated with lower mortality, with a 10% lower mortality for every 5-U increase in BMI (31). In a large, randomized controlled trial of 7,599 patients with symptomatic HF with either reduced or preserved systolic function, patients with underweight/normal BMI had higher mortality than overweight

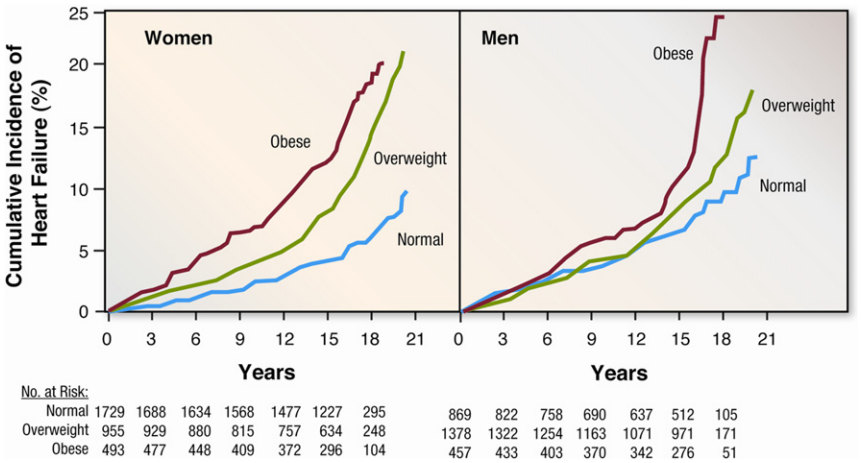

Figure 2 **Risk of Heart Failure**

Prevalence of heart failure in 5,881 Framingham participants according to obesity status. Reprinted, with permission, from Kenchaiah et al. (25).

and obese HF patients. However, this increased mortality was primarily in those without evidence of volume overload and peripheral edema (32).

Mechanisms for obesity paradox in HF. The reasons for the obesity paradox in CV diseases, including HF, remain unclear and are somewhat difficult to reconcile (Table 2). Because HF is a catabolic state, obese patients may have more metabolic reserve, and there is no doubt that cachexia is associated with adverse prognosis in HF (33,34). Various cytokines and neuroendocrine profiles of obese patients may be protective (1,33,34). Adipose tissue is known to produce soluble tumor necrosis factor-alpha receptors, which could have a protective effect in obese patients with both acute and chronic HF by neutralizing the adverse biological effects of tumor necrosis factor-alpha (35). Studies have also demonstrated that overweight and obese patients generally have a reduced expression of circulating natriuretic peptides, which Mehra et al. (36) also demonstrated in HF, potentially leading to obese patients becoming symptomatic and thus presenting earlier at less severe stages of HF, although it could be argued that these circulating natriuretic peptides are not very functional. Additionally, obese patients may have an attenuated response of the RAAS, which may also lead to a better prognosis (1). Moreover, obese patients generally have higher levels of arterial BP than do their leaner counterparts, which could theoretically lead to tolerating more cardioprotective medications, such as beta-blockers, RAAS inhibitors, and aldosterone antagonists at higher doses, all of which could lead to an improved prognosis (1). In addition, higher circulating lipoproteins in obese patients may bind and detoxify lipopolysaccharides that play a role in stimulating the release of inflammatory cytokines, all of which may serve to protect obese HF patients (1,37). Certainly, most of the HF studies that demonstrated the obesity paradox expressed body habitus by BMI alone, which did not provide for the most accurate reflection of adipose tissue. However, as mentioned previously, several studies demonstrated that the obesity paradox in HF persists with the measurement of percent body fat and central obesity (1,28,29).

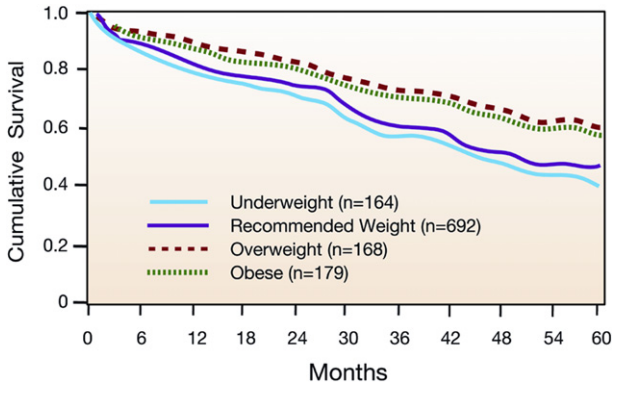

Figure 3 **Obesity and Survival in Heart Failure**

Risk-adjusted survival curves for the 4 body mass index categories at 5 years in a study of 1,203 patients with moderate to severe heart failure. Survival was significantly better in the overweight and obese categories. Reprinted, with permission, from Horwich et al. (27).

Investigators suggested that unmeasured confounding factors might have impacted prognosis, although the obesity paradox was consistent in most studies of other CV disease, including HTN, CHD, and atrial fibrillation, in addition to HF (1). However, none of the studies accounted for nonpurposeful weight loss before study entry, and certainly such patients would be expected to have a poor prognosis (1,33). Finally, there was also evidence that lower levels of atrial natriuretic peptides were associated with increased muscle mass in the overweight and obese patients compared with

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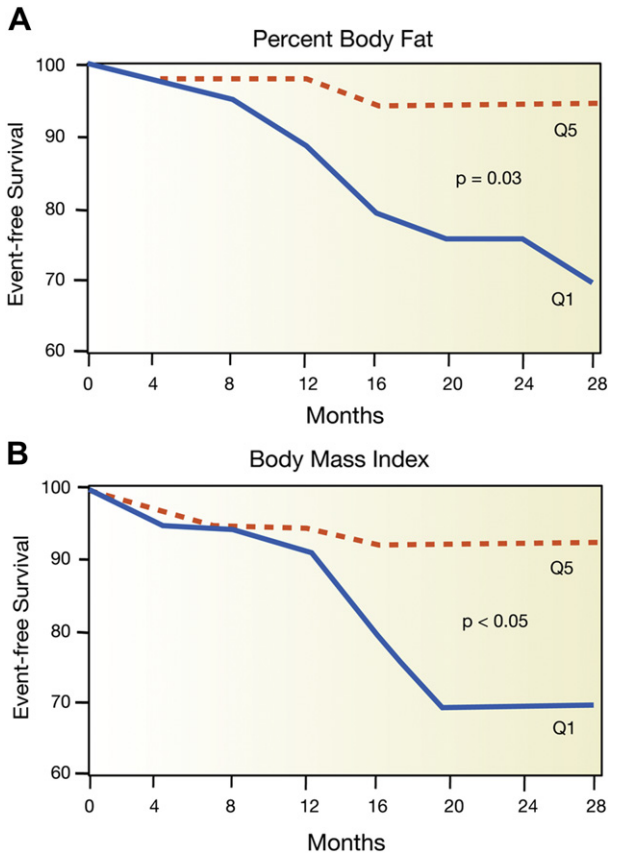

Figure 4 **Body Composition and Heart Failure Prognosis**

Freedom from cardiovascular death or urgent transplantation in patients in quintiles (Q) 1 and 5 for percent body fat **(A)** and body mass index **(B)**. Reprinted. with permission, from Lavie et al. (28).

those who were normal weight (38). and that higher fat mass was associated with more muscle strength (39). Certainly, studies demonstrated the important association between lean mass, muscle strength, and subsequent survival, which might be applied to patients with advanced HF (40,41). Additionally, evidence suggested that in cohorts of CHD, those patients with high cardiorespiratory fitness did not seem to have an obesity paradox (42–44), whereas an obesity paradox was present in those with low fitness using BMI, percent body fat, and central obesity (44). Lavie et al. (45) recently demonstrated that this same relationship between cardiorespiratory fitness and subsequent prognosis also applied to patients with HF.

Table 2 **Potential Reasons for the Obesity Paradox in Heart Failure**

A. Nonpurposeful weight loss
B. Greater metabolic reserves
C. Less cachexia
D. Protective cytokines
E. Earlier presentation*
F. Attenuated response to renin-angiotensin-aldosterone system
G. Higher blood pressure leading to more cardiac medications
H. Different etiology of heart failure
I. Increased muscle mass and muscular strength
J. Implications related with cardiorespiratory fitness

*Due to lower atrial natriuretic peptides, restrictive lung disease, venous insufficiency, and so on.

Assessing Prognosis in HF: Focus on CPX

Assessing prognosis in HF may be more difficult in obese patients with HF. Diagnosing HF may be more difficult in obese patients, who are more likely to have dyspnea due to restrictive lung disease and deconditioning and more likely to have peripheral edema due to venous insufficiency, which theoretically could lead to a "mistaken identity" in HF.

Performing an exertional assessment may assist in the diagnosis of HF, and if confirmed, clearly portends prognostic value. The 6-min walk test recently demonstrated prognostic value in a large HF cohort, although the impact of obesity on its ability to predict events was not assessed; however, some patients whose weight prevented the performance of formal treadmill testing could potentially perform this assessment (46). However, CPX remains the gold standard aerobic assessment and a clinical standard in patients with HF (47). The clinical utility of data derived from CPX has evolved from the exclusive assessment of peak Vo_2 to a broader multivariate approach that now includes markers of ventilatory efficiency, which is primarily expressed as the minute ventilation/carbon dioxide production (VE/VCo_2) slope (47,48). Aside from the ability of CPX to help discern the mechanism(s) of exercise intolerance, numerous studies clearly demonstrate the strong prognostic value of peak Vo_2 and the VE/VCo_2 slope as well as their ability to gauge disease severity in HF (48,49). Thus, although there are numerous approaches to assess prognostic outlook in patients with HF, CPX is perhaps 1 of the most valuable assessment tools for this purpose. When assessing peak Vo_2 and the VE/VCo_2 slope in the clinical setting, a multilevel approach is preferable to a dichotomous classification. Four-level classification schemes have been established for both peak Vo_2 (50) and the VE/VCo_2 slope (51). Patients who are ventilatory class IV (VE/VCo_2 slope $\geq$45) and Weber class D (peak Vo_2 <10 ml O_2 $kg^{-1}min^{-1}$) are considered to be at an advanced stage of HF and have an extremely poor prognostic outlook. Conversely, patients who are ventilatory class I (VE/VCo_2 slope <30) and Weber class A (peak Vo_2 >20 ml O_2 $kg^{-1}min^{-1}$) are considered to have only a mild degree of disease severity and an excellent prognosis. Additionally, correcting peak Vo_2 for lean as opposed to total body mass appears to provide better prediction of HF events, although lean peak Vo_2 has not been compared with the VE/VCo_2 slope in HF patients (52).

Previous research also demonstrated an obesity paradox in a large HF cohort referred for CPX (53,54). Moreover, there appeared to be some differences in the obesity paradox according to HF etiology. Arena et al. (54) found the prognosis was only improved in obese patients with ischemic

HF, whereas both obese and overweight nonischemic HF patients had a similar, more favorable, outcome compared with normal weight patients. However, despite the obesity paradox, the robust prognostic value of CPX variables, in particular the VE/VCo_2 slope, appears to be well preserved. This appears to be the case when considering patients according to BMI classification (i.e., normal weight, overweight, obese) or HF etiology. In both instances, CPX continues to provide significant prognostic information.

In patients with CHD, in whom an obesity paradox was also demonstrated, it appeared that a higher aerobic capacity ameliorated this phenomenon (42–44). In other words, patients who were normal weight but had high aerobic fitness had a favorable prognosis. Recently, Lavie et al. (45) demonstrated the same effect in HF, demonstrating an obesity paradox only among HF patients with low cardiorespiratory fitness (e.g., peak Vo_2 <14 ml O_2 $kg^{-1}min^{-1}$). However, Chase et al. (53) demonstrated that BMI, although a significant univariate predictor, was not a significant marker in a multivariate model that included the VE/VCo_2 slope, left ventricular ejection fraction, and absolute peak Vo_2. These findings indicated that key CPX responses that were favorable might eliminate the impact of the obesity paradox in HF. Future research should continue to investigate the interaction between body composition and aerobic exercise performance as it relates to prognosis in this chronic disease population.

Obesity and Heart Transplantation

Whether obesity is a contraindication for HT remains an ongoing debate. Any form of open-heart surgery in obese patients is associated with poor wound healing, increased risk of infection, pulmonary complications, and lower extremity thrombosis (55–57). One study reported that obese patients had a higher 5-year mortality compared with normal weight or overweight HT recipients (58). Moreover, obese HT recipients had a shorter time to high-grade acute rejection and an increased annual high-grade rejection frequency, but had a similar incidence of cardiac allograft vasculopathy compared with normal-weight recipients (58). In a multicenter (Cardiac Transplant Research Database [CTRD]) study of 4,515 HT patients (59), pre-operative obesity (>140% of ideal body weight [PIBW]) was associated with increased risk of infection in either sex (>54 years of age), with an elevated 4-year mortality in men and a trend toward increased mortality in women. Conversely, pre–HT BMI and PIBW were not associated with a higher incidence of acute rejection or cardiac allograft vasculopathy after HT. The International Society for Heart and Lung Transplant (ISHLT) registry demonstrated that recipient weight was not a risk factor for 5-year survival (60). Another single-center study evaluated 114 overweight and obese patients, defined as a BMI $\geq$27 kg/m^2 (61). A review of the United Network for Organ Sharing demonstrated that obese recipients waited longer and had a lower probability of receiving a donor heart after listing, despite similar short-term survival (62).

In general, it seems that pre-HT BMI $\geq$30 kg/m^2 or PIBW $\geq$140% are associated with poor outcome after HT. The ISHLT guidelines support the notion that reduction in body weight by decreasing BMI or PIBW is necessary to achieve optimal post-HT outcomes. In general, severe obesity (i.e., BMI >40 kg/m^2) may be a contraindication for HT, and in most candidates, every effort must be made to achieve a BMI $\leq$30 kg/m^2 or PIBW $\leq$140% before HT (63).

Obesity and Mechanical Circulatory Support Devices

Concerns that obesity reduces mechanical circulatory support (MCS) outcomes have not been uniformly supported. MCS may allow an obese patient to successfully lose weight during support or wait long enough for a suitable donor if they are listed for HT. However, adverse effects of obesity, such as increased driveline infection rates, have created concern (64).

Generally, clinical trials have excluded a BMI of $\geq$40 kg/m^2, limiting data in this area (64).

A recent report, however, showed that cachexia (i.e., BMI <16 kg/m^2) was worse than obesity in defining post-MCS outcomes, once again indicating a possible obesity paradox (65). The investigators demonstrated a poor prognosis in patients with lower BMI and increased sepsis after MCS (65). Interestingly, the highest BMI seemed to demonstrate better outcomes with infectious complications in this observational study.

Obesity is not a contraindication to using a continuous-flow LVAD, and these devices can provide sufficient cardiac output support to meet the metabolic demands of obese patients. Because cardiac cachexia (i.e., BMI $\leq$22 kg/m^2) is associated with higher mortality and sepsis (65,66), it is important to improve nutrition before and after LVAD implantation. Lockard et al. (67) showed that patients with a pre-albumin level of $\leq$15 mg/dl at 2 weeks after LVAD implantation had a significantly greater risk of in-hospital mortality.

The decision of implanting a LVAD for weight-loss purposes in obese patients with end-stage HF should be undertaken with a multidisciplinary team approach that includes physicians, nurses, dieticians, exercise physiologists, and perhaps, bariatric surgeons (64).

Intentional Weight Reduction in HF

The most effective long-term therapy for the hemodynamic alterations and structural cardiac changes associated with obesity is intentional weight loss (i.e., weight loss via structured dietary and exercise programs or bariatric surgery) (1,2–4,7,8,10,12,15,16,19,20,68). In class II and III obese patients, intentional weight reduction results in decreased total and circulating blood volume, LV stroke volume, cardiac output, LV stroke work, and LV work (3,4). Intentional

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weight loss is often accompanied by a decrease in mean arterial pressure in hypertensive obese patients (2–4). The effects of intentional weight loss on systemic vascular resistance and pulmonary hemodynamics are more variable (3). In particular, substantial intentional weight loss in class II and III obese patients has not consistently lowered LV end-diastolic or pulmonary capillary wedge pressure, either at rest or during exercise (3,4). Studies of class III obese patients have reported decreases in LV end-diastolic chamber size and LV mass (7,8,10,68,69). In such patients, LV mass decreases primarily in those with LVH (7,8). This appears to be related in part to improvement in LV loading conditions (7,8). The reported effect of intentional weight loss on LV morphology in class I obese patients is more variable.

Although LV end-diastolic and pulmonary capillary wedge pressures do not consistently decrease following intentional weight reduction, noninvasive indexes of diastolic filling have generally improved following weight loss in class I, II and III obese patients (15,16,68,69). In 1 study of class III obese patients, this improvement occurred only in those with LVH (8). In another study, LV diastolic filling improved in normotensive, but not in hypertensive obese patients (16). In a study that employed tissue Doppler imaging of the mitral annulus in obese patients, peak myocardial velocity during diastole significantly increased with intentional weight loss (18). Because LV systolic function is usually normal in uncomplicated obesity, intentional weight loss produces little change in LV ejection phase indexes (19). In 1 study of class III obese subjects, substantial weight loss produced a significant increase in LV fractional shortening in those with depressed pre-weight loss LV systolic function (20).

Despite this evidence and considering the previously described obesity paradox, the major HF societies have variable recommendations regarding intentional weight reduction interventions in HF. The American Heart Association recommends intentional weight loss in HF only with BMI >40 kg/m^2, the Heart Failure Society of America for BMI >35 kg/m^2, and both the European Society of Cardiology and the Canadian Cardiovascular Society recommend weight loss for BMI >30 kg/m^2. Moreover, none of the major societies recommend weight loss for overweight patients with HF. The reasons for these variations are likely related to lack of data regarding intentional weight loss and long-term prognosis in HF. Clearly, studies are needed to determine the short- and long-term impact of intentional weight loss in various patients with HF, including the safety and long-term efficacy of bariatric surgery, which appears to be safe and effective in very small studies (70), and optimal body composition in patients in different stages of HF.

Conclusions

Obesity clearly has adverse effects on CV structure and leads to systolic and, especially, diastolic LV dysfunction. Not surprisingly, the prevalence of HF is markedly increased in obesity. Nevertheless, many studies demonstrate a strong obesity paradox in HF, in which obese patients with HF have a better prognosis than do their leaner counterparts, and this obesity paradox is apparent with BMI, percent body fat, and central obesity. Weight reduction clearly has beneficial effects on cardiac structure and function, but only limited data are available to base current recommendations for intentional weight loss in HF. Nevertheless, we feel that the "weight" of evidence supports intentional weight reduction in HF, especially for those with more significant obesity, although clearly better clinical studies are needed to define optimal body composition in patients with HF.

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