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Diogo Filipe Pereira Damas

Interação entre obesidade e insuficiência cardíaca: ponderando a evidência

Interplay between obesity and heart failure: weighing the evidence

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Interplay between obesity and heart failure: weighing the evidence

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e aquele(s) que sabem quem são

Interplay between obesity and heart failure: weighing the evidence

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Abstract

The obesity epidemic has been associated with increased risk of metabolic and cardiovascular diseases. Excess adipose tissue has several direct and indirect effects that adversely impact hemodynamics, cardiac morphology and function, including systolic and diastolic dysfunction that can ultimately lead to the onset of heart failure (HF). Nevertheless, many studies have observed an obesity paradox in large cohorts of HF, where overweight and obese patients have a better prognosis compared with normal-weight patients. Despite intense research on the protective effects of fat mass, the exact mechanisms behind the obesity paradox in HF are still unclear. Some of the explanations include the impact of cardiac cachexia, the role of neuro-humoral pathways, the protective profile of adipose tissue and higher tolerability for cardioprotective drugs. Recent studies have highlighted that lean mass and cardiorespiratory fitness are associated with lower cardiovascular risk and can modulate the relationship between obesity and mortality. However, it is important to consider the potential involvement of comorbidities, confounders and selection bias in the assessment of the validity of the obesity paradox. Although purposeful weight loss improves cardiovascular abnormalities related with obesity and reduces HF symptoms, the lack of large randomized clinical trials focusing on the effects of weight loss prevents robust clinical recommendations on optimal body weight in obese patients with HF.

Keywords: obesity, heart failure, obesity paradox, body composition, weight loss

Resumo

A epidemia da obesidade está associada a um risco aumentado de doenças metabólicas e cardiovasculares. O excesso de tecido adiposo tem efeitos diretos e indiretos que afetam negativamente a hemodinâmica, morfologia e função cardíaca, incluindo disfunção sistólica e diastólica que podem levar ao desenvolvimento de insuficiência cardíaca (IC). Contudo, vários estudos demonstraram um paradoxo da obesidade em coortes de IC, em que os doentes com excesso de peso ou obesos têm melhor prognóstico comparativamente com doentes de peso normal. Apesar da investigação intensa acerca dos efeitos protetores do tecido adiposo, o mecanismo exato subjacente ao paradoxo da obesidade continua desconhecido. Algumas das hipóteses incluem o impacto da caquexia cardíaca, o papel das vias neuro-humorais, o perfil protetor do tecido adiposo e maior tolerabilidade para fármacos cardioprotetores. Estudos recentes destacam que a massa magra e o fitness cardiorrespiratório estão associados a diminuição do risco cardiovascular e são capazes de modular a relação entre obesidade e mortalidade. Porém, é importante considerar o potencial envolvimento de comorbilidades, confundidores e viéses de seleção na avaliação da validade do paradoxo da obesidade. Apesar da redução intencional de peso melhorar as alterações cardiovasculares relacionadas com a obesidade e reduzir os sintomas de IC, a ausência de ensaios clínicos randomizados de larga escala focados nos efeitos da perda de peso atrasa a produção de recomendações clínicas robustas acerca do peso corporal adequado aos doentes obesos com IC.

Palavras-chave: obesidade, insuficiência cardíaca, paradoxo da obesidade, composição corporal, perda de peso

Introduction

Obesity has reached epidemic proportions in Western countries since 1980[1, 2], and is considered the second leading cause of preventable death following tobacco use.[3] Worldwide, the prevalence of obesity has nearly doubled in more than 70 countries with estimates that more than 1.4 billion adults aged 20 years and above were overweight in 2008, representing 35% of the world population at the time (11% were obese). Sixty-five (65)% of the world's population lives in countries where overweight and obesity kills more people than underweight.[4] This problem is expanding to the developing countries which are experiencing a high prevalence of obesity similar to trends that were reported by developed countries in the earlier years of this epidemic.[5, 6]

Obese individuals have increased risk of developing cardiovascular diseases (CVD), including arterial hypertension (HTN), coronary artery disease (CAD) and heart failure (HF).[7, 8] Additionally, obesity is associated with direct effects on hemodynamics and cardiac function that predispose to the onset of systolic, and especially, diastolic dysfunction, potentiating the risk of HF.[9-13] However, several studies have shown that overweight and obese HF patients, particularly class I and II, have lower mortality and better prognosis compared to normal-weight HF patients.[8, 11, 14-19] This reverse epidemiology has been termed the "obesity paradox" in HF, and many different hypotheses have been suggested to explain this paradox.[11, 16, 20]

In this review, we firstly assess the impact of obesity in cardiovascular health as well as the adverse effects on hemodynamics, cardiac structure and ventricular function. Also, the role of obesity on the development and prevalence of HF is reviewed, along with the various studies that reported the obesity paradox in HF. We will also analyze all the proposed hypotheses to explain the paradox and the major arguments against it. Finally, we will discuss the role of weight loss in obese patients with HF and its importance on unveiling the obesity paradox.

1. Obesity and Cardiovascular Risk

The World Health Organization defines obesity as "an abnormal or excessive fat accumulation to the extent that represents a risk to health".[2] The rising prevalence of obesity to epidemic levels and the increasing health care costs associated with this disease has led to the establishment of guidelines to address the identification, evaluation, and treatment of overweight and obesity. Based on the evidence available, body mass index (BMI), which is calculated as body weight in kilograms divided by height in meters squared, is the chosen method to evaluate weight categories because of its simplicity and practicality.[21] Therefore, BMI categories are defined as normal weight (BMI of 18.5–24.9 kg/m^2), overweight (25–29.9 kg/m^2), and obese (≥30 kg/m^2) for individuals over 18 years of age. Even though the etiology of the obesity epidemic has been intensely debated, it is widely accepted that increased adiposity is the result of a chronic positive energy balance, with energy intake exceeding energy expenditure.[7]

There are substantial adverse cardiovascular effects of overweight and obesity. In fact, obesity is associated with the development of several cardiovascular risk factors such as dyslipidemia, atherosclerosis, type 2 diabetes mellitus (DM) and metabolic syndrome as well as increased lifetime risk of CVD.[21, 22] It is also a major independent risk factor for CVD, such as CAD, atrial fibrillation and HF.[7, 8] Overweight and obese patients have consistently demonstrated a higher prevalence of CAD, and the Framingham study showed that 23% of CAD in men and 15% of CAD in women were attributable to excess adiposity.[23] Another analysis of patients from the Framingham cohort study, with a follow-up of up to 48 years, concluded that there is an obvious dose-dependent relationship between all-cause mortality and the number of years lived with obesity; for every additional 2 years with obesity, CVD mortality risk increased by 7%.[24] Khan *et al.* performed a study with a long follow-up period from 1964 to 2015, and confirmed that obesity is associated with a significantly increased risk of CVD morbidity and mortality compared with normal BMI individuals.[22] As a result, the American Heart Association identified maintenance of a normal BMI as 1 of the 7 key components of ideal cardiovascular health. Despite new therapeutic strategies and intense research investigation, the current status and future projections of excess body weight on a global level are disconcerting.[25]

Thus, it is well documented that obesity can be considered a risk marker, in that it is associated with a higher prevalence of comorbidities such as DM, dyslipidemia and metabolic syndrome, which themselves can also be viewed as risk factors for the development of CVD (figure 1).[26]

2. Obesity Cardiomyopathy

Obesity is associated with hemodynamic alterations that contribute to the development of cardiac structural abnormalities and left and right ventricular dysfunction.[9-11, 13] Thus, obesity cardiomyopathy can be defined as HF caused predominantly or entirely by obesity and occurs mainly in class III (BMI ≥40 kg/m^2) or super-obese (BMI ≥50 kg/m^2) patients who have usually been severely obese for more than 10 years.[10, 11, 27, 28] Recent studies using animal models, revealed that several neurohormonal and metabolic disturbances associated with obesity contribute to these alterations.[9-13] Obesity is considered an independent risk factor for CAD, HTN and DM, which lead to the development of ischemic, hypertensive and diabetic cardiomyopathy, respectively, and can potentiate the rise of HF.[12, 29, 30] Considering all these combined effects, overweight and obesity can be a risk factor or a dominant cause of HF and should probably be considered an even match with CAD and HTN for the development of HF.[31]

Obesity cardiomyopathy is a complex interplay of multiple direct and indirect pathophysiologic factors related to obesity, making it difficult to differentiate individual pathways or to fully assess the contribution of obesity to the development of HF. Duration and severity are the two most important factors for functional and structural impairment of the cardiovascular system.[9] Obesity-induced “meta-inflammation”, which consists in a chronic low-grade inflammatory state, can gradually lead to multiorgan dysfunction. Myocardial dysfunction can be a direct injury by inflammatory mediators as well as a result of other organs dysfunction caused by meta-inflammation.[29, 32] On the other hand, obesity is a state of insulin resistance that leads to decreased glucose uptake and promotes the use of fat as a preferential source of energy in cardiomyocytes. This creates higher levels of toxic products of fat oxidation and oxidative stress originating mitochondrial dysfunction, apoptosis and loss of functional myocardium.[33, 34] The pathological increased fat accumulation in cardiomyocytes induces the development of “cardiac steatosis,” representing a state of myocyte hypertrophy and interstitial fibrosis associated with both diastolic and systolic dysfunction.[33, 35, 36] The combination of abnormal hypertrophy and scarring of the myocardium leads to structural and functional loss of myocardial cells, producing obesity-induced cardiomyopathy.

The pathophysiology of HF is very complex and involves ventricular remodelling, neurohormonal system activation, systemic inflammation and abnormalities in calcium fluxes which are important for the development and progression of this disease.[37] In particular, obesity is capable of producing a wide range of hemodynamic alterations that predispose to modifications in cardiac structure and ventricular function, including left

ventricle (LV) dilation, eccentric or concentric LV hypertrophy, LV systolic and diastolic dysfunction, and right ventricle dysfunction.[38] The excessive adipose tissue can produce an increase in central and total blood volume and stroke volume, associated with a decrease in systemic vascular resistance that can ultimately increase the cardiac output.[10, 39-45] Initially, the increase in cardiac output associated with obesity was attributed to the increased fat mass. However, blood flow per unit of adipose tissue is relatively low (2 to 3 ml/min) and is insufficient to fully explain the elevated cardiac output state.[10, 11] Thus, the increased blood volume now seems to be the result of the increased amount of lean mass (LM) seen in most obese patients.[40, 46, 47] Although obesity is defined by a higher amount of fat mass, the classic obesity phenotype usually presents with preserved or increased LM, being the skeletal muscle the main component.[39, 40, 46, 48, 49] The fact that blood flow requirement for skeletal muscle mass is significantly higher comparing to fat mass is particularly relevant.[50] Therefore, the increased skeletal muscle mass, and not fat mass, associated with an increase in blood flow and volume appear to be the main factors responsible for the higher stroke volume seen in the obese HF patients. Since heart rate usually remains unaltered or just moderately increased due to sympathetic system activation in obesity[10, 11, 46], the increase in cardiac output is predominantly attributed to an increase in LV stroke volume and cardiac work, which have been reported to be elevated in obese patients.[10, 11, 44, 45, 51]

This sustained increase in cardiac output due to increased preload together with systemic hypertension and other metabolic factors predispose initially to LV dilatation followed by a compensatory hypertrophic response evident at both cellular and organ level.[48, 52] In fact, LV hypertrophy was the predominant pathological finding in obese patients.[9, 11, 47, 53-55] Studies using echocardiography or cardiac magnetic resonance imaging to assess LV mass have consistently reported significantly higher values of LV mass in all classes of obesity compared with lean controls.[10-13, 56] Those with HF (predominantly class III obese patients) had significantly greater LV mass than similarly obese patients without HF. Traditionally, the increase in LV chamber size and LV mass has been attributed to adverse LV loading conditions relating to altered hemodynamics.[10-13, 56] In addition to hemodynamic alterations and duration of obesity, certain metabolic (insulin resistance with hyperinsulinemia, leptin resistance with hyperleptinemia) and neurohormonal abnormalities (activation of the renin-angiotensin-aldosterone and sympathetic nervous systems) that occur commonly in obesity have been shown to produce increased LV mass in animal models and, to a lesser extent, in humans.[10, 11] Multiple recent studies have reported that among obese subjects with abnormal LV geometry, concentric LV remodelling or hypertrophy occurs more commonly than eccentric LV hypertrophy.[10, 54, 57-59]

Several non-invasive studies of LV diastolic function in obesity have consistently shown impairment of LV diastolic filling or relaxation comparing to lean controls.[10, 11, 38, 60-62] Moreover, the incidence of LV diastolic dysfunction increases progressively with higher classes of obesity, from 12% in class I to 35% in class II and to 45% in class III obesity.[38] Interestingly, even though impairment in diastolic function and increased filling pressures were considered to be the result of the increased LV mass, it has been documented that obese patients may present with diastolic dysfunction without LV hypertrophy[63, 64], suggesting the presence of alternative mechanisms. As with LV mass, duration of obesity appears to contribute to impairment of LV diastolic filling.[65] Contrary to LV diastolic function, most studies assessing LV systolic function in obesity have reported normal or even supranormal values of LV ejection fraction.[10-13, 66-68] Even studies with obese patients that have shown a significantly lower LV systolic function comparing to lean controls, it was only marginally in most cases and still within the normal range.[10-13, 67-69]

Moreover, the increase in BMI in obese patients correlates with increased left ventricular filling pressure and pulmonary capillary wedge pressure[10-13, 43, 45, 56, 70]. Consequently, this leads to an elevation of pulmonary artery pressure and an increase in right ventricular end-diastolic and right atrial pressures. This pathological process is facilitated by the presence of obstructive sleep apnea syndrome and obesity-hypoventilation syndrome, which are very common in severely obese patients.[10, 11] The presence of hypoxemia and pulmonary artery vasoconstriction in these patients contribute to pulmonary arterial hypertension, although LV failure remains the predominant cause.[10, 11]

Although the alterations mentioned above in cardiac performance occur in class I and class II obesity, they are most pronounced in class III and super-obesity. Figure 2 summarizes the pathophysiology of obesity cardiomyopathy.

3. Obesity and Heart Failure

Over the last decades, despite several important advances in mortality-reducing therapies in cardiology, the incidence of HF and acute decompensated HF hospitalizations has been on the rise.[71] In the same period, the incidence of obesity has also been steadily increasing, with approximately 35% of the United States population being obese and 69% either overweight or obese.[4] There is a well-established

association between obesity and HF and with the rising prevalence of both conditions makes this connection a crucial target for therapy and prevention.

The largest epidemiological study to assess the risk of HF in obesity resulted from the Framingham Heart Study.[72] Kenchaiah *et al.* analyzed 5881 participants and showed that obesity is an independent risk factor for the development of HF. It was also demonstrated that for each increment of 1 kg/m^2 in BMI, there was an increase in the risk of HF of 7% in women and 5% in men, with a graded increase in HF prevalence across the BMI categories.[72] Comparing with normal BMI subjects, obese individuals had double the risk of HF. For women, the hazard ratio was 2.17 (95 % confidence interval (CI), 1.51 to 2.97); and for men, the hazard ratio was 1.90 (95 % CI, 1.30 to 2.79). The increased risk of developing HF was independent of age, alcohol intake, cigarette use and comorbidities, including but not limited to DM, HTN and history of myocardial infarction. Similarly, the Physician's Health Study of 21,094 men without known CAD showed an independently associated increase of HF in overweight and obese subjects comparing to normal weight.[73] An analysis of the Atherosclerosis Risk in Communities cohort of over 14,000 individuals performed by Loehr *et al.* demonstrated obesity to be an independent risk factor for the development of HF, after adjusting the covariates.[74] Another large study of over 59,000 individuals from Finland showed a graded association between BMI and HF risk, with adjusted hazard ratios of HF for overweight and obese patients as compared to normal weight of 1.25 (95 % CI= 1.12–1.39) and 1.99 (95 % CI= 1.74–2.27) in males, and 1.33 (95 % CI= 1.16–1.51) and 2.06 (95 % CI= 1.80–2.37) in females.[75] In a study of 74 morbidly obese patients by Alpert and colleagues, nearly a third of the subjects had clinical evidence of HF and the probability of HF increased substantially with increasing duration of obesity, with prevalence rates exceeding 70% at 20 years and 90% at 30 years.[27] Thus, it has been reported that severity and duration of obesity strongly impacts the onset of HF (figure 3).

Heart failure is considered a complex clinical syndrome that results from any structural or functional impairment of ventricular filling and/or ejection of blood.[76] This problem affects over 38 million people worldwide with almost 915,000 new cases every year and is the most common reason for hospital admissions in patients over 65 years.[37, 77] Although the survival rate in HF has improved in recent years, the mortality is still very high; more than 30% of patients die within 5 years of diagnosis.[37, 77] Moreover, near half of the HF patients have a reduced LV ejection fraction (LVEF) or systolic dysfunction (HF with reduced ejection fraction [HFrEF]), while the other half presents with preserved LVEF (HF with preserved ejection fraction [HFpEF])[37, 76] usually characterized by diastolic dysfunction. Furthermore, despite sharing similar signs and symptoms, such as fluid retention, shortness of breath and exercise intolerance, these 2 forms of HF (HFpEF and HFrEF) have not only differences in LVEF but also in epidemiology, pathophysiology

and clinical characteristics, which are highlighted by the fact that therapeutic strategies in HFrEF have failed to improve outcomes in HFpEF.[37, 76-79]

HFpEF is characteristically more prevalent in women and associated with obesity with up to 85% of patients with HFpEF being obese[10, 52], while in HFrEF, obesity prevalence is normally lower than 50%.[80, 81] A study by Pandey *et al.*[82] has shown that the increase in risk of HFrEF is lower compared to the significant increased risk for HFpEF in the obese population. Overall, approximately 38% of patients with HF are obese.[52] The link between obesity and HFpEF has received much attention in recent years with an 'HFpEF obesity phenotype' being proposed, but the pathophysiological mechanisms behind this association are still unclear.[10, 39-42, 46, 83-85] Body composition, rather than BMI, may be a better predictor of outcomes once HF is stablished.[86]

"Diastolic HF" or HFpEF has been increasing steadily in the past few decades and consists in impaired diastolic function associated with preserved LVEF and no major coronary artery, valvular, or arrhythmic disease.[52, 78, 87] Since the majority of HFpEF patients are obese and metabolic alterations are frequently present, it has been proposed that obesity and diastolic dysfunction are causally linked.[78, 87] Multiple hypotheses have been proposed including a potential role for cardiodepressant factors produced by the adipose tissue, like proinflammatory cytokines such as interleukin (IL) 1β, tumour necrosis factor α (TNF-α), and IL-18[88], which have been demonstrated to induce diastolic dysfunction in animal models.[79, 88-91] Pilot studies using targeted anti-inflammatory treatment have reported promising results in HF, including HFpEF.[89, 92, 93]

Since obesity is usually the result of an unhealthy diet, recent studies found that a high-sugar (30% of total calories) and high-saturated fat (12.8% of total calories) diet typical of Western countries (Western diet) can promote cardiac diastolic and systolic dysfunction in animals models[94, 95], supporting the potential link between diet-induced inflammation and cardiac dysfunction. These sugars and fats can potentiate proinflammatory pathways responsible for the synthesis of IL-1 and IL-18, which have well-known cardiodepressant properties.[96, 97] Moreover, returning to a healthy diet created significant improvements in cardiac function, showing the major ability of diet to modulate both systolic and diastolic function.[94, 95, 98-100]

It should be highlighted that physical activity appears to influence the association between obesity and HF. In addition to the increasing BMI, the Physicians Health Study revealed that lower level of physical activity was associated with an increased risk of HF, with the highest relative risk of HF observed in obese men and physically inactive compared to lean men and physically active.[73] Similarly, in the Finnish cohort discussed above, the protective effect of physical activity was demonstrated at all levels of obesity, reducing the risk of HF in adjusted models by 21–32%.[75]

4. Obesity Paradox and Heart Failure

The relationship between obesity and HF can be characterized as intriguing to say the least. On one hand, several studies have shown that obesity is an independent risk factor for the development of HF[72, 101] and on the other hand many large studies have demonstrated that overweight and obese patients are associated with lower mortality and have better short- and intermediate-term prognosis compared with their leaner counterparts in cohorts with established HF.[8, 11, 14-19] Thus, this apparent paradoxical relationship as been termed the "obesity paradox in HF".[7, 86, 102] The reverse epidemiology association was first described by Horwich *et al.* in 2001, which demonstrated that overweight and obese patients had the best HF prognosis while underweight and normal BMI patients had the worst prognosis, and this association has been consistently supported by several studies and meta-analyses.[18] This phenomenon has been particularly observed in obese class I and II HF patients and many different hypotheses have been proposed to explain this paradox.[11, 16, 20]

Oreopoulos *et al.*[103] performed a meta-analysis using 9 observation studies that included nearly 30,000 patients and showed that overweight and obese patients with HF had a reduction in CVD mortality (19% and 40%, respectively) and all-cause mortality (16% and 33%, respectively) compared to HF patients without elevated BMI. Another study by Clark *et al.*[104, 105] revealed that higher BMI and waist circumference (WC) were associated with improved survival in HF patients, with the best survival in those with both high BMI and high WC. A study in patients with acute decompensated HF across four continents showed an 11% decrease in 30-day mortality and a 9% decrease at 1 year for every 5 kg/m^2 increase in BMI, confirming an obesity paradox, mostly confined to older patients, those with reduced cardiac function, less metabolic diseases and recent onset HF.[106] A recent meta-analysis of 6 studies (n = 22,807), with patients who had chronic HF (HFrEF and HFpEF) and a mean follow-up of almost 3 years, revealed that rehospitalizations, adverse events, including CV mortality, and all-cause mortality were highest in low BMI group (normal and underweight) and lowest in overweight group (figure 4).[15] Specifically, overweight patients had the lowest total mortality (relative risk [RR]: 0.78; CI: 0.68–0.89) compared with those who were normal weight, while underweight patients had the highest total mortality (RR: 1.27; CI: 1.17–1.37) and subjects with class II or higher obesity had an intermediate prognosis with lower total and cardiovascular mortality despite having increased HF hospitalizations.[15] A secondary analysis of the Meta-Analysis Global Group in Chronic Heart Failure (MAGGIC) included 31 studies, randomized controlled trials and observational studies, demonstrated an association between BMI and mortality in HFrEF and HFpEF, with the

lowest mortality rate being registered in class I obese patients (figure 5).[14] Similarly, another study has shown lower or similar 30-day mortality risk for obese patients with both HFrEF and HFpEF.[107]

A secondary analysis of the Candesartan in Heart failure - Assessment of mortality and morbidity (CHARM) trial which initially reported that candesartan decreased cardiovascular events and hospitalization for HF patients with a LVEF <40%[108], further revealed a J-shape association of the relationship of BMI and cardiovascular prognosis, with the highest protection attributed to obese subjects.[80] Similarly, *post-hoc* analysis of the Irbesartan in Heart Failure with Preserved Ejection Fraction (I-PRESERVE) trial showed that overweight patients experienced less mortality and hospitalizations for HF over a follow-up period of 49 months with excess mortality in underweight and severely obese patients.[109] The Chronic Heart Failure Analysis and Registry in the Tohoku District (CHART) study in japanese HF patients demonstrated that the underweight group, defined by the investigators as BMI <18.5 kg/m^2, was as similar as the severe obesity group.[110]

Conversely, fewer studies have studied the association between BMI and mortality in acute heart failure (AHF). A study using the Acute Decompensated Heart Failure National Registry (ADHERE), a prospective cohort that collected clinical data and intra-hospital outcomes of over 100,000 patients hospitalized for AHF in the United States, was the first to show that the obesity paradox controls the association of BMI and in-hospital mortality, with a 10% decrease of mortality when moving to a higher BMI range.[111] Utilizing a similar cohort, Fitzgibbons *et al.* reported that the survival benefit of obesity on mortality extends to 3 months after AHF discharge.[112] In a japanese HF registry (JCARE-CARD), a high BMI, defined as being ≥23.5 kg/m^2 in japanese patients, portrayed better mortality in AHF comparing to a BMI range of 20.3–23.49 kg/m^2.[113] Interestingly, the Acute Heart Failure Global Survey of Standard Treatment (ALARM-HF) study showed that overweight but not obese patients were associated with less intra-hospital mortality, although this benefit vanished after correcting for confounders.[114] Another important finding that was reported by Khalid *et al.* showed that subjects with prevalent obesity before the HF development and diagnosis still had lower mortality and better long-term survival compared with normal BMI subjects, suggesting that the obesity paradox occurs even when obesity manifests several years before the HF.[115]

Despite the cumulative evidence that supports the existence of the obesity paradox, there is also evidence that argues against it. For instance, a study evaluated the importance of BMI in a large cohort of diabetic patients with HF and rejected the existence of an obesity paradox in this population.[116] Thus, similar to exercise tolerance, diabetes may be a stronger outcome predictor than obesity, which advocates for the fact that assessing obese HF patients without accounting for their metabolic

status or exercise tolerance may be misleading.[117] Similarly, a secondary analysis using data from the Rural Education to Improve Outcomes in Heart Failure (REMOTE-HF) trial[118], which was designed to improve self-care in HF patients living in rural areas, found that obesity was an independent predictor of longer survival in patients without diabetes, however this association vanished in HF patients with concomitant diabetes.[119] One epidemiological study, with a follow-up of 25 years, compared cardiovascular mortality between normal-weight participants and overweight or obese participants with and without risk factors associated with obesity (HTN, DM and dyslipidemia).[120] Of these 3 risk factors, the presence of diabetes alone was not associated with an increase in cardiovascular mortality among overweight or obese participants compared with normal-weight participants without the 3 obesity-related risk factors. Nonetheless, in patients with diabetes and hypertension or dyslipidemia or both, the cardiovascular mortality was significantly higher in overweight and obese participants.[120] Although diabetes is an important comorbidity associated with obesity and poor outcome in HF, in most studies relating BMI with survival, the presence of diabetes was controlled for or not even considered.[14, 19, 105, 118, 121] Altogether, these results indicate that among HF patients with metabolic abnormalities, diabetes may be an effect modifier factor of the relationship between obesity and survival and may attenuate or even cancel the protective effect of adipose tissue on cardiovascular mortality.

A study of 3811 patients with systolic HF from the Cleveland Clinic revealed that the obesity paradox 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.[17, 122] On the other hand, although most studies have indicated an obesity paradox in HF independent of gender, this study found that overweight female patients had a significant 16% lower mortality with a multivariate model that also supported a differential gender impact of BMI on mortality.[17, 122] As it was previously stated, the Framingham Heart Study showed that for every 1 kg/m^2 increase in BMI, there was a 5% increase in men and a 7% increase in women for the risk of HF.[46, 72] In a study from Hu *et al.* that followed 59,178 patients for 18 years, similar hazard ratios for HF were reported at normal, overweight and obese patients for both men (1.00, 1.25 and 1.99; [p<0.001], respectively) and women (1.00, 1.33 and 2.06; [p<0.001], respectively).[75] Thus, despite the apparent similar risk, multiple studies have shown a female advantage in HF, which is still not completely understood.[122-125] A recent study examined HFrEF patients who had undergone cardiopulmonary exercise testing, in which overweight and obese males had worse outcomes than normal weight males, but overweight females had a significant survival

benefit.[122] The female gender has been associated with a greater fatty-acid metabolism and lower myocardial glucose utilization, which may be related to an estrogen effect and may indicate an increased use for energy production comparing to males.[122, 123, 126] This sexual dimorphism has been previously described between CVD mortality and higher circulating adiponectin levels, which are higher in males than females.[122, 127, 128] All of these results taken together, may indicate that the increase in adipose tissue in females may offer mortality advantages in HF.

Overweight and obese patients with HF have some important characteristics that are more prevalent in these groups comparing to normal-weight HF groups. Obese HF patients are usually younger, more likely to be female, have higher prevalence of HFpEF, lower prevalence of smoking and alcohol abuse, more probable to have DM, HTN and dyslipidemia, higher levels of pre-HF C-reactive protein and significantly lower BNP levels than normal/underweight HF patients.[129-131] Other interesting data suggest that the obesity paradox may be confined to overweight and class I obesity and not apply to class III or super-obesity.[46, 132] In these patients, prognosis should be guided by CVD risk manifestation that is associated with very poor prognosis and prompt every effort to treat and prevent class III obesity.[46]

Therefore, there has been increasing concern in the cluster of clinical, sociodemographic and lifestyle factors associated with obese HF patients. Indeed, there is evidence of potential interactions across gender, HF phenotype, metabolic profile and behavioural factors that affect body composition, exercise capacity and quality of life.[14, 122, 133] Taken together, all these variables can modify the “reverse epidemiology” association between BMI and mortality in HF patients, suggesting that the obesity paradox may only be valid under certain conditions. Furthermore, this survival benefit of obesity has been identified in a wide range of cardiovascular diseases, such as myocardial infarction, hypertension, peripheral vascular disease, atrial fibrillation, aortic stenosis and patients with acute coronary syndromes.[134-140] There is also evidence that the obesity paradox exists in patients with pneumonia, chronic obstructive pulmonary disease, chronic respiratory insufficiency, chronic renal disease, cirrhosis, stroke, cancer and DM.[141-148] In conclusion, the obesity paradox has been consistently reported in HF patients in a wide range of clinical subpopulations across gender, age range, geographical location, presence or absence of comorbidities[149] and using different measures of adiposity, like BMI, WC, triceps skinfold thickness and waist-hip ratio (WHR).[16, 18, 104, 105, 127, 150-152]

5. Physiology of the Obesity Paradox

The mechanisms behind the obesity paradox in HF remain unclear and are not completely understood, although many potential hypotheses have been proposed.[11]

"Cardiac Cachexia" was one of the first possible explanations for the improved survival in overweight and obese HF patients. Certainly, HF is considered a chronic catabolic state associated with fat and lean mass (LM) loss which carries a very poor prognosis in these patients.[11, 129, 153] For instance, 50% of HF patients with cachexia (defined as nonintentional documented weight loss of at least 7.5% of previous normal weight over 6 months) had died at 18 months follow-up.[16] Some recent studies showed that fat mass loss may precede LM loss, and may be an indicator of the onset of declining HF prognosis.[154, 155] Thus, since advanced HF is particularly associated with cachexia, overweight and obese patients with increased adiposity may have extra metabolic reserves that protect against the progressive catabolic state of their disease.[8, 39, 156] Malnutrition in the context of cardiac patients is usually attributed to anorexia, dysphagia, eating difficulties, depression, functional disabilities and social isolation. This profound catabolism due to wasting and increased metabolic demands causes unintentional weight loss that is associated with an extremely high burden of disease.[154] Cardiac cachexia, characterized by progressive lean and fat mass loss, is the expected consequence of this disease-related malnutrition.[8] Despite several studies demonstrating the poor prognosis of cachexia in HF, most of them did not differentiate intentional from unintentional weight loss and generally were unable to account for non-purposeful weight loss before study entry.[11, 154] A more recent study revealed that overweight and obesity prior to the diagnosis of HF are associated with improved survival up to 10 years after the onset of disease, suggesting that weight loss caused by the enhanced HF catabolic state may not completely explain the apparent protective effect of increased BMI in HF patients.[115]

Another explanation relies on neuro-humoral pathways to justify the obesity paradox in HF. Adipose tissue promotes the production of soluble TNF-α receptor that can play a role in neutralizing the biological activity of TNF-α, which is a powerful inflammatory cytokine, and confer a protective advantage in HF patients.[11, 157, 158] It has also been documented that obese patients present with reduced adiponectin levels and suppressed catecholamine response that can be associated with improved prognosis.[20] In obese patients, higher levels of circulating lipoproteins have the ability to bind and detoxify bacterial lipopolysaccharide (LPS or endotoxin), which is a strong stimulator for the immune system, as well as neutralize the circulating cytokines.[11, 158, 159] Thus, this mechanism has been called the endotoxin-lipoprotein hypotheses which advocates that

high cholesterol levels are beneficial in HF patients because of the capacity of lipoproteins to modulate the inflammatory immune response.[151]

The adipose tissue is not only a lipid storage depot but also an endocrine organ capable of producing a wide range of substances termed adipokines, which might have protective effects on the myocardium and partially explain the obesity paradox.[12, 160] Adiponectin, which is inversely associated with BMI and obesity but increased in HF patients, has direct and indirect beneficial cardiovascular effects and is an important predictor of morbidity and mortality.[161-163] The most well-known adipokine is leptin or "satiety hormone". Obesity is associated with selective leptin resistance that may influence myocardial function and impact many parameters related to obesity and HF.[163-165] Thus, there is evidence that leptin is involved in cardiac hypertrophy, stimulation of glucose and fatty-acid metabolism in the heart, protection against steatosis and prevention of apoptosis.[163, 166] Resistin is another adipokine that can impact the sympathetic system activity and interact with leptin.[167] Other studies have shown some interactions between adipokines and ghrelin or "hunger hormone", which is mostly produced by the gastrointestinal tract and has some potential protective cardiovascular effects, including impact on heart rate, increase in myocardial contractility, improved exercise capacity and energy metabolism in myocardium, blood pressure reduction, inhibition of sympathetic system activity and protection of endothelial cells.[163, 168-170] Ghrelin inhibits angiotensin II-induced cardiomyocyte apoptosis and AT1 receptor upregulation preventing HF.[171] On the other hand, this adipokine can have a compensatory mechanism in HF patients by enhancing appetite and promoting weight gain in cachexia.[163, 168]

Visceral adipose tissue expansion has been associated with hyperinsulinemia, increased fatty acid circulation, high somatostatin and reduce ghrelin combined with a reduction in endogenous growth hormone secretion which has direct cardiac effects.[172, 173] Additionally, adipokines released by the myocardium or the larger pericardial fat mass may have important autocrine and paracrine effects in obese patients.[174] Another explanation states that the fat (especially subcutaneous fat) or muscle tissue can produce insulin-sensitizing and anti-inflammatory substances like adipokines and myokines that may have beneficial cardiovascular effects.[157, 175]

Furthermore, overweight and obese HF patients may become symptomatic earlier than normal-weight HF patients due to symptoms produced by the increased body weight (i.e., extreme deconditioning, musculoskeletal, among others) such as exertional dyspnea or edema. Also, obese patients usually have multiple comorbidities, like DM and HTN, representing a high-risk screening group. This early presentation of disease may lead to an apparently prolonged lifetime, consisting in a lead time bias, where overweight and obese HF patients present in an earlier stage in HF timeline.[8, 83, 115, 156]

Thus, these patients are then subjected to optimal pharmacological treatment and management as well as lifestyle modifications that could result in the improved survival observed in the obesity paradox.[102, 103, 122] Moreover, obese individuals with a higher comorbidity risk profile may pass away prior to HF diagnosis, meaning that only the "healthiest" obese patients may survive long enough to develop HF and lead to a disproportionally favourable prognosis in the remaining high BMI population, the "healthier survival effect".[156]

It has been demonstrated that overweight and obese HF patients have decreased expression of circulating natriuretic peptides, like BNP, and may offer some insight into high BMI patients presenting at earlier and less severe HF stages.[11, 176-178] BNP is a neurohormone produced and released by cardiomyocytes in response to excess stretching of the ventricular wall and is a significant predictor of mortality and prognosis in HF.[106, 179-181] Natriuretic peptides including BNP have adaptative functions in HF including increased diuresis and decreased vascular resistance.[182-184] Therefore, low levels of BNP may contribute to early symptomatic presentation of fluid accumulation symptoms, such as edema and dyspnea, in obese patients with HF comparing to non-obese patients, which in turn could lead to early cardioprotective treatment.[176, 185] Moreover, atrial natriuretic peptides have some metabolic functions including activation of lipolysis, which may lead to weight loss and cachexia in advanced HF patients.[185-187]

On another level, obesity is generally associated with increased blood volume and higher blood pressure that allow for obese HF patients to tolerate higher doses of cardioprotective drugs, such as β-blockers and renin-angiotensin system inhibitors (ACEI or ARA) compared to leaner patients.[8, 11] Thus, the use of greater disease-modifying drugs and tolerance to optimal medical therapy is associated with better prognosis in obese patients with HF.

The observation that skeletal muscle mass (SMM) has a major protective role in chronic diseases, like cancer and diabetes, led to the hypothesis that it may also exert a beneficial effect in HF patients.[188] Thus, if increased fat mass (FM) characterizes obesity, a condition with reduction in LM and SMM is defined as sarcopenia and is associated with cardiometabolic abnormalities and poor outcomes in HF.[2, 188-190] More than suggesting an obesity paradox, the association between low BMI and worse clinical outcomes in CVD has led to the proposal of a "lean paradox".[7, 191, 192] This hypotheses is based on evidence supporting that low BMI and low body fat percentage (BF%) are independent predictors of worse outcomes and increased mortality risk, with the unintentional weight loss being associated with high morbidity and mortality for several diseases, especially HF.[8, 46, 193]

On the other hand, subjects presenting with excess FM (obesity) and a decreased LM or SMM (sarcopenia) are labelled with sarcopenic obesity, a state which brings together

both body composition abnormalities and is associated with enhanced cardiometabolic risk that is worse than either obesity or sarcopenia alone.[194, 195] A recent meta-analysis that included more than 35 000 patients revealed that sarcopenic obese patients had 24% increased risk for all-cause mortality compared to nonsarcopenic obese patients.[196] A study examining HF patients according to BMI and mid-upper arm circumference as a surrogate for muscle mass, revealed that patients with low BMI and low arm circumference had significantly higher mortality, whereas low BMI and high arm circumference did not.[197] These results showed that the combination of BMI and arm circumference assessment improved mortality prediction as well as the fact that muscle mass may alter the association of increased adiposity and survival in HF patients.[198] To the date, the major obstacle with the use of body composition phenotypes is the absence of standard thresholds for FM and LM in the definition of both obesity and sarcopenia, respectively.

Obese individuals usually present with increase in FM but also an increase in LM and SMM.[2, 48] Despite being involved in hemodynamic and cardiac abnormalities that increase de risk of HF, obesity that presents with increased skeletal mass can exert protective effects and be associated with better survival in HF. Considering the pathophysiology of HF regarding reduced or inadequate cardiac output and higher systemic vascular resistance[76], obese individuals with preserved or increased skeletal mass may have increased stroke volume and cardiac output as well as reduced systemic vascular resistance, being associated with improved tissue perfusion and thus better prognosis comparing to leaner counterparts.[10, 11, 39, 40, 46, 50] A retrospective analysis in HFpEF reported an initial analysis suggesting that increased BMI and FM were associated with lower mortality, however, after adjusting for lean mass index, these associations were not observed.[199] These results indicate that the protective component of high BMI and body weight was not fat mass but lean mass.

LM and SMM, particularly appendicular muscle mass, have been recognized as major determinants of cardiorespiratory fitness (CRF) in HF patients. Although it has been neglected for CVD risk stratification, it is well known that CRF correlates with health status and represents a potent prognostic factor in calculating an individual's CVD risk, particularly in HF patients.[200] For instance, a meta-analysis of 33 studies revealed that for each 1 metabolic equivalent increase in CRF, all-cause and CVD events reduced by 13% and 15%, respectively.[201] Besides many studies reported the independent effects of obesity and CRF on mortality, a study by Barry and colleagues focused on the joint association of CRF and BMI and showed that unfit individuals had twice the mortality risk regardless of BMI, while fit overweight or obese individuals had similar mortality risks compared to normal weight individuals.[202] Thus, it has been proposed that high levels of CRF can largely neutralize the significant adverse effects of obesity and other

CVD risk factors, including HTN, type II DM and metabolic syndrome, which has been described as the "Fat but Fit" phenomenon.[46, 203, 204]

In fact, many observational studies revealed that CRF status significantly shifts the effects observed in the obesity paradox.[205, 206] These studies reported that when patients are stratified according to CRF level using a peak VO_2 cut-off of 14 mL/kg/min, the protective effects of the obesity paradox disappear in HF patients with preserved CRF level (figure 6).[207, 208] This highlights the more prominent impact of CRF, rather than BMI, in HF prognosis and that an increased degree of LM and CRF are independently associated with better clinical outcomes. Other studies have supported the fact that CRF may be a stronger predictor of CVD outcomes than obesity and could independently reduce mortality regardless of BMI.[202, 209, 210] Therefore, it has been demonstrated that CRF has a dose-dependent, inverse association with HF risk, and is considered one of the best predictors of outcome, regardless of age, sex, body composition and chronic diseases.[3, 211, 212] Some authors even suggest that while obesity may only have a protective effect in short- and medium-term follow-up, CRF may have more long-term protective effects. Taken together, these findings suggest that increasing LM, especially appendicular LM, and maintaining or improving CRF are effective and proven beneficial therapeutic strategies to apply in HF patients across all weight groups.[86, 198, 203]

Thus, the potential beneficial effects of fat and muscle mass have been the basis for the numerous pathophysiological mechanisms proposed to explain the obesity paradox. In other words, the increased muscle and fat observed in obese patients with HF may be associated with better outcomes and prognosis than non-obese patients because this type of body composition may promote a beneficial advantage. Table 1 summarizes the several mechanisms associated with the obesity paradox.

6. Evidence against the Obesity Paradox

Even though mounting evidence supports the obesity paradox in HF patients, there are several factors that should be taken into account when considering these findings and assessing their validity in clinical practice. These include the use of BMI to classify obesity, the presence of comorbidities, confounders and selection bias.

Obesity is mostly commonly defined by using BMI, considered to be a simple and inexpensive measurement to apply in clinical setting.[8] Despite its usefulness, BMI is considered a rough and incomplete guide to excess weight since individuals with similar BMI may have different degrees of adiposity and it does not account for fat distribution

or body composition.[213] Thus, the utility of BMI has been questioned for its incapacity to differentiate between fat, lean and muscle mass, indicating that this is an inaccurate measurement at the individual level because different body compositions are associated with different cardiometabolic profiles.[3, 86] For this reason, more accurate measures to identify excess fat have been developed, such as WC and BF%, which have been used to determine all-cause mortality and incident CVD.[214, 215] Therefore, it would be expected that more accurate measures of adiposity would be considered stronger predictors of mortality than BMI.[216] However, Ortega *et al.* compared BMI and other indicators of fat mass, like BF%, fat mass index and fat-free mass index, and showed that BMI still remained a stronger predictor of cardiovascular mortality comparing to more accurate, complex and expensive methods.[217] Studies have demonstrated that BMI is highly correlated with WC and WHR and all have been shown to produce comparable estimates.[218, 219] For example, in adult population, the correlation between BMI and WC reported a range from 0.85 to 0.94 and the correlation between BMI and BF% ranges from 0.72 to 0.84.[218] Thus, it is reasonable to assume that BMI will continue to be used as gold-standard of body composition because of its utility and simplicity in assessing the effects of fat mass in cardiovascular pathology. In addition to BMI and BF%, other measures of increased adiposity, like WC and WHR have also shown consistent results compatible with the obesity paradox in HF.[46]

Another important aspect when talking about the obesity paradox is to consider the presence of comorbidities. Patients with CVD are usually older and have a higher burden of comorbidities which can independently affect mortality.[220] A study that analyzed over 296 000 subjects showed that obesity was associated with higher CVD risk and this association was even strengthened after excluding participants with comorbidities, implying that the presence of comorbidities may be a confounder for the relationship between BMI and mortality.[214] Furthermore, low weight patients with comorbidities, like chronic obstructive pulmonary disease, chronic kidney disease and malignancy, may reflect the severity of disease and be related to increased CVD risk. Instead of obesity being a protective advantage, weight loss promoted by illness results in lower weight and BMI prior or after CVD diagnosis due to an increased catabolic state and decreased metabolic reserves. This phenomenon reflects reverse causality proposing that pre-existing illness triggers unintended weight loss and increased mortality risk among lower BMI groups, being a possible explanation for the obesity paradox and is minimized when accounting body weight throughout the life course.[221-225] The incidence of weight loss and mortality risk are usually higher in individuals suffering from an illness, but this form of bias is capable of shifting the estimates toward the null, or potentially past the null, giving rise to the obesity paradox.[223, 225] However, many studies have demonstrated that, even when excluding subjects with history of cancer, CVD or those who died early

in the follow-up, the mortality risk does not change significantly across BMI categories.[226-230]

Confounding has been another source of bias to the relationship between obesity and mortality in HF. One of the first identified factors was smoking, being associated with two important biases in mortality analyses: reverse causation and confounding.[221] As discussed above, reverse causation in this situation occurs because smoking is associated with higher risk of cardiovascular and non-cardiovascular comorbidities that predispose to unintentional weight loss. On the other hand, current smoking is a source of confounding because is associated with both lower BMI and increased mortality rates. A study from NHANES III and 1999-2010 found that mortality risks were significantly increased in the overweight and obese groups (hazard ratio: 1.51; 95% CI 1.07, 2.15), confining the analysis to never-smokers.[231] Another analysis with 1.46 million individuals from the general population reported that restriction to never-smoking further strengthened the mortality risk in overweight (hazard ratio: 1.13 [95% CI 1.09, 1.17]) and obese groups (hazard ratio ranging from 1.88 to 2.51 for BMI from 30.0 to 49.9 kg/m^2) comparing to normal BMI reference group.[232] However, analytic evidence showed that controlling for smoking has minimal effects on the BMI-mortality association and omitting smokers leaves results qualitatively unaltered.[233, 234] For instance, in models adjusted for smoking, the BMI associated with minimum mortality was 24.3 kg/m^2, while not adjusting for smoking resulted in a minimum mortality BMI of 25.0 kg/m^2.[233] Moreover, residual confounding from unmeasurable or unaccountable variables could shift the inverse association between BMI and mortality in HF, especially in observational, retrospective and secondary data analysis studies.

Finally, the presence of different types of selection bias has been proposed to potentially explain the obesity paradox.[235] Banack and Kaufman were among the first authors to suggest that the obesity paradox may be explained by a simple selection bias, known as collider-stratification bias.[236] In other words, conditioning on a variable affected by exposure and sharing common causes with the outcome can distort the relationship between exposure and outcome and even reverse the direction of association from harmful exposure to protective effect.[237-240] Obesity is associated with the development of CVD, which is a stablished predictor of mortality, but can also directly influence mortality risk.[241] Therefore, conditioning on a collider affected by exposure and outcome, in this case HF, can produce a spurious association between obesity and mortality in HF patients, potentially creating the obesity paradox. This type of selection bias has already been demonstrated formally and empirically in a study of the obesity paradox in patients with dysglycemia.[242] A bias analysis study demonstrated that after correcting for the selection bias, the protective effects of obesity on mortality disappeared among individuals with CVD in the NHANES III cohort, which is consistent

with the fact that collider stratification bias can explain the obesity paradox.[243] However, the authors state that these results may be consistent with several other scenarios and do not reject the possibility of alternative explanations. Moreover, a study by Glymour and Vittinghoff[244] revealed that the collider bias must be very strong to reverse the causal effect and Banack and Kaufman[245] concluded that even though the reversal is possible, strong associations within the selection bias pathway are required. Although the collider stratification bias may be an important factor when considering the paradoxical protective effects of obesity on HF mortality, is questionable that selection bias can fully explain the obesity paradox.[246] Another potential source of bias resides in the fact that considering the higher risk of fatal cardiovascular events, obese patients can die at a younger age and are less likely to be included in studies, resulting in the potential for survival bias.[247] Additionally, data from the Cardiovascular Lifetime Risk Pooling Project revealed that overweight and obese subjects have earlier onset of disease and higher cardiovascular events.[22] After the diagnosis of HF, obese patients appear to live longer because they are more likely to be diagnosed with HF at a younger age, resulting in the appearance of an obesity paradox. This phenomenon is described as lead-time bias and is similar to a manifestation described in cancer screening studies.[221]

7. Effects of weight loss

Intentional weight loss achieved by implementing lifestyle modifications, like diet and exercise, can reduce the risk of developing metabolic syndrome and type II DM and decrease CVD risk, being the best therapeutic approach in obese patients.[46, 248-251] Despite the beneficial effects of obesity in HF, intentional weight loss in these patients remains controversial.

Except for severe obesity, some studies have reported increased mortality with worse overall prognosis in overweight and obese patients that experienced weight loss.[46, 158, 252] A study by Pocock *et al*, that addressed the effects of weight changes after baseline assessment in HF, showed increasing mortality with the degree of weight loss even in obese subjects, regardless of initial BMI.[193] However, this study did not distinguish between intentional or unintentional weight loss and body composition assessment was not performed in order to evaluate if weight loss was a product of reduction of FM or more importantly loss of LM. Since cachexia is often the potentiator of weight loss in HF[153, 253], rapid weight reduction can be associated with decreased LM, which may

increase the onset of sarcopenia and sarcopenic obesity, paradoxically increasing mortality risk.[254, 255]

Purposeful weight loss may be the most effective long-term therapy for improving hemodynamic alterations and cardiac structure and function abnormalities associated with obesity, particularly in the setting of HF, independent of age, sex, BMI and comorbidities.[3, 9, 11, 256] Thus, weight loss reduces total blood volume, blood pressure, myocardial oxygen consumption, LV mass, LV stroke volume, LV work and CO in patients with class II and III obesity.[11, 27, 44, 257, 258] Bariatric surgery has also reported that weight loss caused improvements in LV geometry as well as systolic and diastolic function.[11, 46] A recent trial in obese patients with HFpEF reported that caloric restriction-induced weight loss induced favourable effects on weight, body composition and CRF. These beneficial alterations manly resulted from changes in body composition, especially FM loss, with increased CRF and no relevant alterations in cardiac function.[259] This suggests the beneficial role of intentional weight loss in HF obese patients, however, the long-term effects of caloric restriction-induced weight loss are still unknown. Moreover, weight reduction showed a nonsignificant trend for lower mortality in overweight and obese patients with CVD risk factor but reported marked improvements in exercise capacity, inflammation, plasma lipids and quality of life.[260]

Therefore, taking in account all the aspects previously discussed regarding the obesity paradox and the evidence of weight loss, the major HF societies have widely variable recommendations on the utility of intentional weight loss strategies, with none recommending weight loss for the overweight patients.[9, 11, 154] The European Society of Cardiology and Canadian Cardiovascular Society recommend purposeful weight loss in HF patients only with BMI ≥30 kg/m^2.[158] However, the European Society of Cardiology recommends management of overweight and obese HF patients as per guidelines for general CVD prevention, acknowledging the gaps in evidence.[261] The more recent HF guidelines from the American College of Cardiology Foundation/American Heart Association do not provide any robust recommendations for purposeful weight loss in any group of HF patients, except for the recognition of very poor prognosis associated with severe, class III obesity.[76] Thus, because of the lack of strong evidence and large-scale trials assessing the role of weight loss in HF, most guidelines do not recommend weight loss in HF but rather suggest avoiding unintentional weight loss.[37] Additionally, we can hypothesize that intentional weight loss targeting FM and preserving or increasing LM can have beneficial effects. However, the correlation of increased fat and greater muscular strength may be one of the reasons for the association between obesity and better outcomes in HF.[198, 262]

Many authors have suggested that because the effects of weight loss in HF are still unclear, interventions focusing on improving CRF in obese HF patients should be

encouraged, regardless of the effect on body weight.[202, 263] Higher levels of CRF are associated with better outcomes and reported to reduce the development of HF.[264, 265] Thus, using the data available, it seems reasonable to recommend intentional weight loss strategies for moderate to severe obese HF patients, with BMI ≥35 kg/m^2.[9, 11, 17] In overweight or mildly obese HF patients, even though weight loss may improve symptoms and outcomes, prevention of weight gain and improving CRF may be preferable goals.[264, 266-268]

Most studies assessing the effects of weight loss are usually retrospective and do not differentiate between “healthy” and “unhealthy” weight loss, producing a wide range of both beneficial and harmful associations. Therefore, large, prospective, randomized controlled trials are much needed to investigate the effectiveness of intentional weight loss and body composition alterations in obese HF patients. Until then, clinical management of heart failure patients must be carefully calibrated to suit individual patient’s profile.[269]

Conclusion

There is undeniable evidence that obesity is a prevalent and independent risk factor for the development of CVD disease, particularly HF. Excess adipose tissue leads to several hemodynamic, cardiac structure and function abnormalities that ultimately predispose individuals to obesity cardiomyopathy which in turn can precipitate the onset of systolic and more frequently diastolic HF. Despite obese individuals having worst outcomes, many studies have shown that overweight and mildly obese HF patients have lower mortality and improved survival comparing to normal weight HF patients, giving rise to the "obesity paradox". Certainly, the existence of the obesity paradox is not a promotion of overweight or obesity, neither is a suggestion that weight gain is beneficial.[270]

Thus, various hypotheses have been proposed to explain the obesity paradox, relying on the potential protective effects of fat and lean mass. However, the underlying mechanism behind this phenomenon is still unknown and it is unlikely that a single hypothesis could be responsible for it, but rather a complex interplay between potential biological effects responsible for the better prognosis in overweight and obese patients with HF. One of the major explanations advocates that, more than representing a beneficial advantage of adiposity, the obesity paradox emphasizes the extremely poor prognosis in lean or underweight patients with HF, with enhanced cardiac cachexia, decreased muscle mass and lower levels of CRF. It is also important to consider that comorbidities, confounding factors and selection bias may influence and limit the interpretation of these findings. In fact, studies that stratify on HF induce an imbalance in the distribution of unmeasured risk factors between obese and non-obese patients. As a simple example, we can divide the causes of HF into those related to obesity and those not related to obesity. If normal weight people develop HF due to nonobese factors and these harmful risk factors have a worse prognosis that obese causes of HF, it is expected that obesity appears protective even if it worsens survival in this diseased population.[271] Therefore, when considering the possible effects of obesity on HF prognosis, we should use a holistic approach bringing together body composition models, additional anthropometric measures (i.e. WC, WHR, BF%) and assessment of LM and CRF, which may help to achieve a better risk stratification in obese HF patients and identify individuals with higher mortality risk (i.e. sarcopenic obesity or low CRF levels).

Finally, weight loss induces many beneficial effects on the cardiovascular and endocrine abnormalities that are frequently reported in obesity. Moreover, weight reduction

causes substantial improvements in body composition and CRF, leading to better survival in obese patients with HF. However, the existence of numerous studies reporting the obesity paradox as well as the positive effects of weight loss in obesity result in unclear evidence about the true consequences of excess adiposity and confusion regarding clinical recommendations for obese HF patients. These recommendations regarding weight loss require solid and conclusive evidence that the obesity paradox is a consequence of true biological mechanisms and not the product of statistical biases.[272] Thus, large randomized clinical trials investigating the effects of intentional weight loss are necessary to guide the management and treatment of obesity in HF and resolve the uncertainty related to the obesity paradox. Additionally, recent research highlighted the importance of considering obesity a time-varying exposure and account for weight trajectory and health over the lifetime to better understand the obesity-mortality relationship.[273, 274] More focused clinical studies assessing the influence of body composition, nutritional status and new risk factors, using the appropriate methods to identify and control bias, are needed.

The existence of the obesity paradox may simply reflect a lack of understanding of the intricate and complex pathophysiology that rules the association between adiposity and CVD. Even so, the reverse epidemiology in HF could be a representation of the evolutionary theory, in that the fittest to survive are not necessarily the most physically active or trained species, but the ones best adapted to their environment.[275, 276] There is enough evidence to anticipate a paradigm shift from the promotion of a single ideal weight towards individualized weight management based on a range of factors, including age, ethnicity and health status.

Disclosure of interest

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Figures and Tables

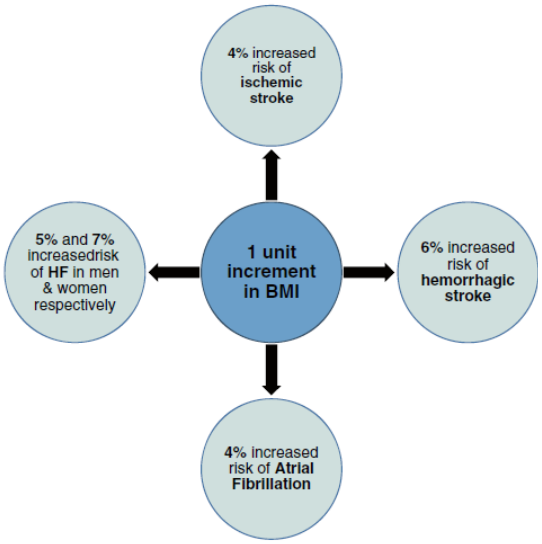

Figure 1. Increased risk of cardiovascular diseases with increase in body mass index (BMI) and body weight. CAD= coronary artery disease; HF= heart failure; SBP= systolic blood pressure; DBP= diastolic blood pressure. Reproduced from Mandviwala et al[26] with permission from Springer Nature.

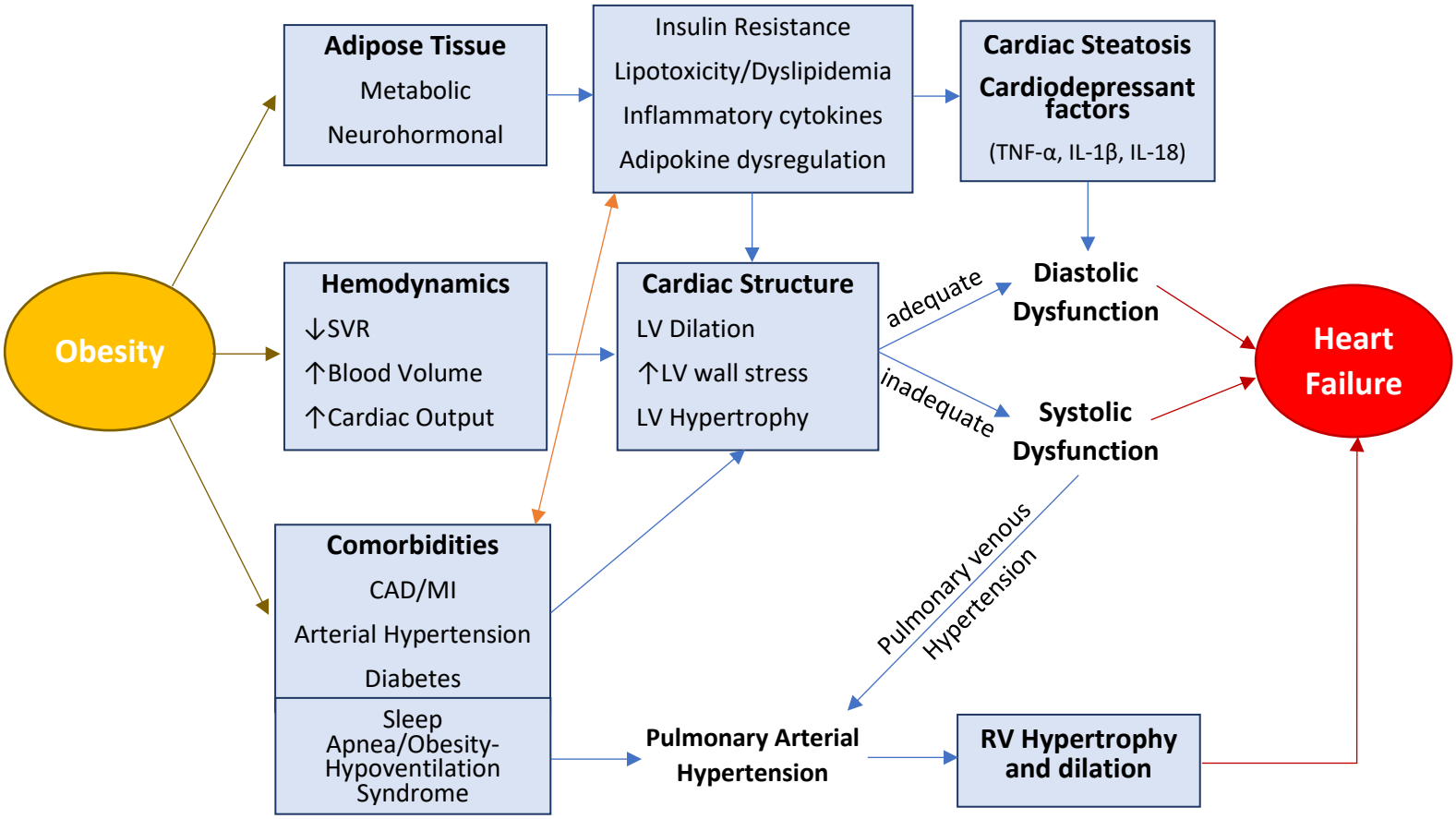

Figure 2. Interplay between various mechanisms that may lead to the development of heart failure in obese individuals. CAD: coronary artery disease; MI: myocardial infarction; LV: left ventricle; RV: right ventricle; SVR: systemic vascular resistance

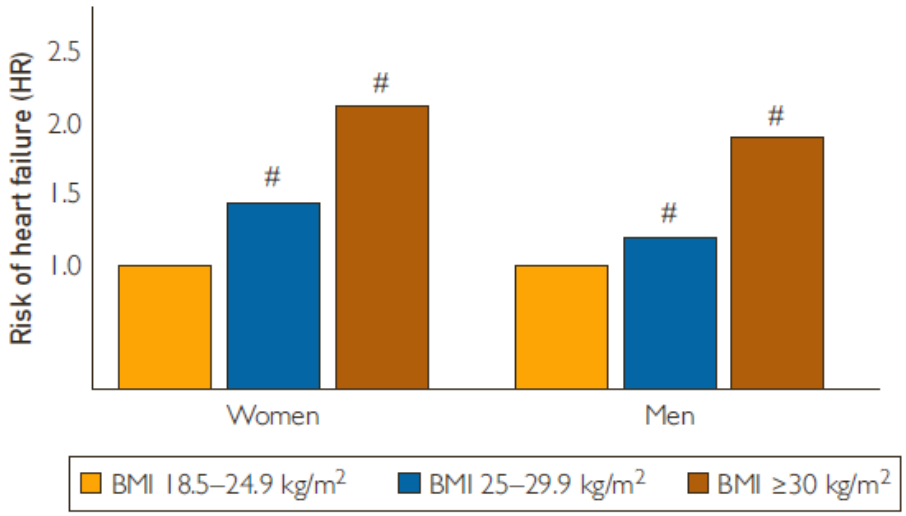

Figure 3. Risk of heart failure according to categories of body mass index (BMI). Considering a BMI of 18.5 to 24.9 kg/m^2 as the reference category, overweight and obese individuals had an increased risk of heart failure with reduced and preserved ejection fraction, described as hazard ratio (HR). # = P<0.01 vs BMI of 18.5 to 24.9 kg/m^2. Reproduced from Carbone et al[96] with permission from Elsevier.

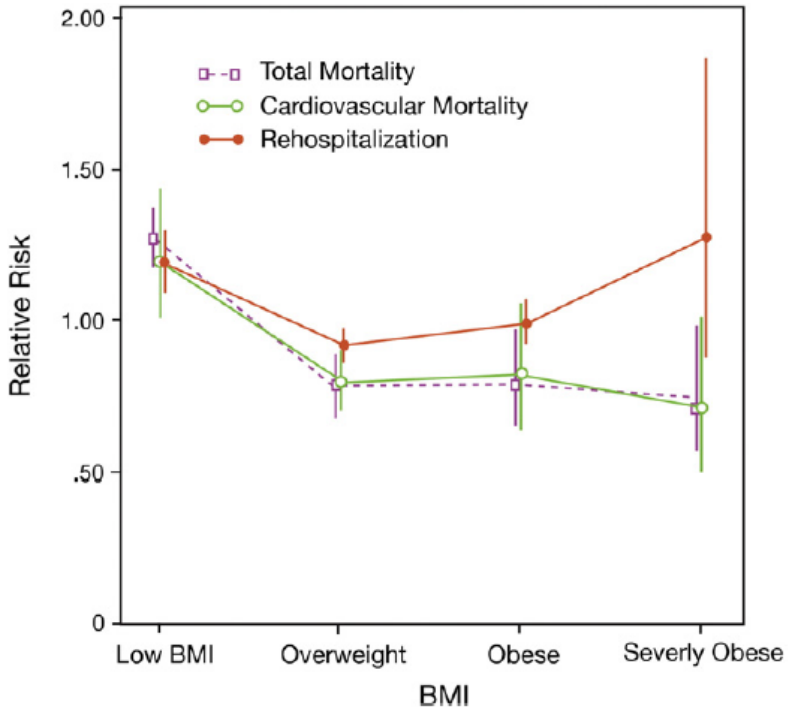

Figure 4. Meta-analysis of six studies (n=22,807) on impact of body mass index on cardiovascular mortality, all-cause mortality and hospitalizations in heart failure. Reproduced from Sharma et al[15] with permission from Elsevier.

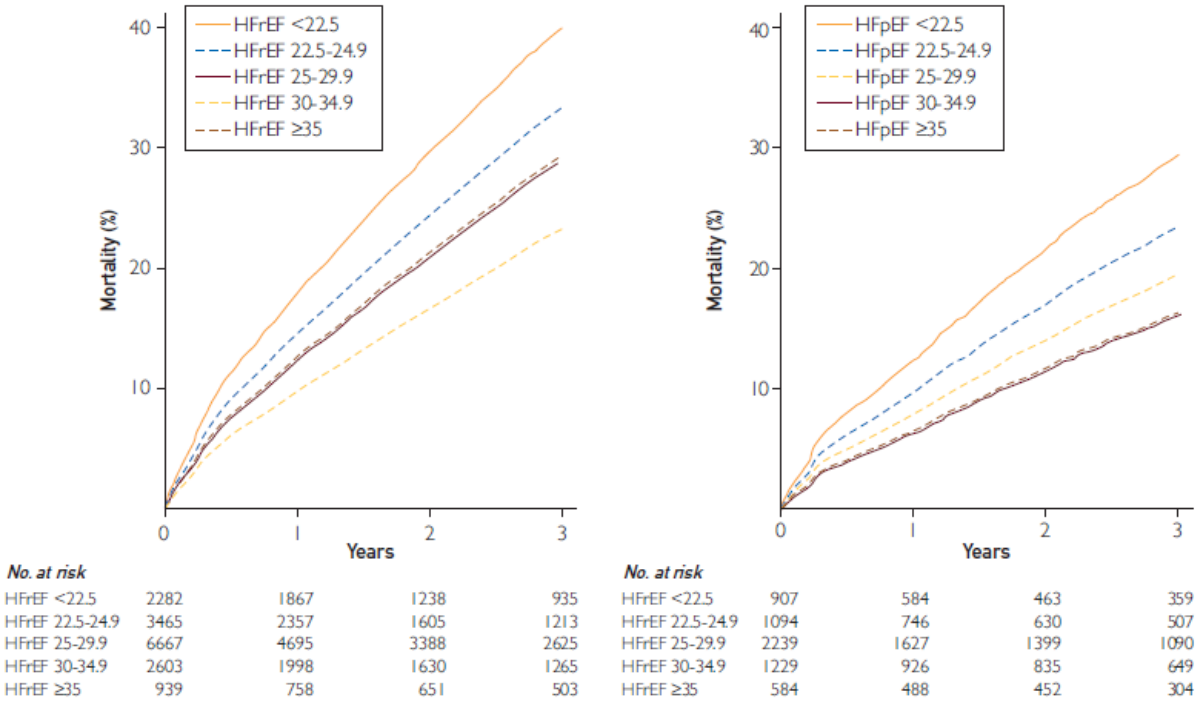

Figure 5. Total mortality stratified by body mass index (BMI) and heart failure (HF). Heart failure is categorized as HF with reduced ejection fraction (HFrEF) or HF with preserved ejection fraction (HFpEF). Patients with HF and higher BMI had a lower mortality rate than those with a lower BMI.
Adapted from Padwal et al[14] with permission from Springer Nature.

Table 1. Potential factors influencing the obesity paradox in heart failure

Factors	Mechanism
1. Less cardiac cachexia	Obesity can reduce the chronic catabolic state that is associated with increase mortalit poor prognosis.
2. Higher metabolic reserves	Increased adiposity may protect against progressive lean and fat loss and disease-related malnutrition.
3. Unintentional weight loss	Cachexia and malnutrition are triggers for unintentional weight loss which is associated with higher mortality.
4. Neuro-humoral pathways	Production of soluble TNF-α receptor, reduced catecholamine response and endotoxin-lipoprotein hypothesis may reduce the inflammation.
5. Protective adipokines	Several adipokines, like adiponectin, leptin and resistin, may have direct and indirect beneficial hormonal and cardiovascular effects.
6. Earlier presentation	Obese patients present with symptoms earlier than normal-weight patients, leading to precocious treatment.
7. Lower natriuretic peptides	Decreased levels of BNP in obesity are associated with early symptomatic presentation and less inadequate adaptative functions.
8. Higher dose of drug therapy	Increased blood volume in obese HF patients allows higher tolerability for cardioprotective drugs such as β-blockers and ACEI.
9. Increased lean mass	Obesity is usually associated with higher lean and muscle mass that increases cardiac output and reduces systemic vascular resistance.
10. “Fat but Fit” phenomenon	Adipose tissue and lean mass promote increased muscular strength and CRF, with long-term protective effects and improved clinical outcomes.

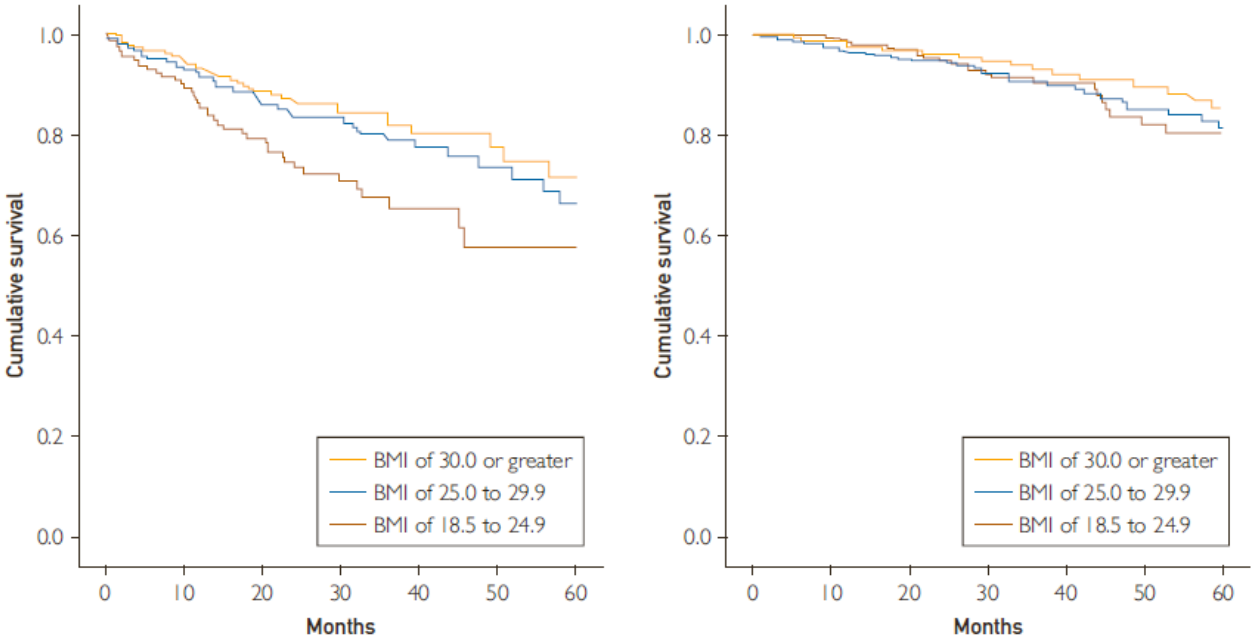

Figure 6. Obesity paradox and cardiorespiratory fitness (CRF). Kaplan-Meier analysis according to body mass index (BMI) in the low CRF group (peak oxygen consumption <14 ml/kg/min) (left) and in the high CRF group (peak oxygen consumption >14 ml/kg/min) (right). This figure describes the absence of the obesity paradox in patients with relatively high CRF compared with those who have low CRF, in which the obesity paradox is apparent. Reproduced from Lavie et al[198] with permission from Elsevier.

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Anexos

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