Heart Failure Reviews (2019) 24:379–385
https://doi.org/10.1007/s10741-018-09766-x

Obesity and heart failure with preserved ejection fraction: a paradox or something else?

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Published online: 5 January 2019

Abstract

Obesity represents one of the most common comorbidities in patients with heart failure and preserved ejection fraction (HFpEF). Studies have shown that obesity is not only a comorbidity, but it could also be an important risk factor for HFpEF development. The mechanisms that connect obesity and HFpEF vary from obesity-induced hemodynamic changes to important biohumoral systems such as adipocitokines, renin–angiotensin–aldosterone and sympathetic nervous systems, natriuretic peptide, and oxidative stress. Studies agree about the negative influence of morbid obesity on cardiac remodeling and HFpEF development. However, there is still no agreement regarding the relationship between body mass index, as the most commonly used parameter of obesity, and HFpEF incidence or outcome in patients who already have HFpEF. The relationship varies from the linear to the U-shaped and, therefore, the "obesity paradox," which refers to the reduced risk in mildly overweight subjects in comparison with normal and underweight individuals, deserves more attention not only in the research but also in the clinical approach to these patients. In the absence of a satisfactory pharmacological approach, which would improve the outcome of this large group of patients, alternative methods such as weight loss and physical activity seem to provide encouraging results. This review article provides a clinical overview of the available data about the mechanisms that connect obesity and HFpEF, the most relevant studies on this topic, clinical relevance of the obesity paradox, and the therapeutic approach including weight loss and physical activity in obese patients with HFpEF.

Keywords Obesity · Heart failure with preserved ejection fraction · Pathophysiology · Obesity paradox · Therapy

Introduction

Heart failure with a preserved ejection fraction (HFpEF) entity has long been unrecognized. On the one hand, reduced left ventricular ejection fraction (LVEF) was conditioned "sine qua non" for the definition of heart failure (HF) for many decades. On the other hand, symptoms in the HFpEF patients were ascribed to comorbidities that are very frequent among HFpEF patients such as obesity, hypertension, and diabetes. Considering the fact that obesity represents an incubator for other comorbidities (diabetes, hypertension, metabolic syndrome), it is quite expected that more than 80% of HFpEF patients are overweight or obese [1]. However, obesity is usually associated with sedentary lifestyle and deconditioning, which is why symptoms in HFpEF were not recognized as HF.

Recent studies have shown significant association between body mass index (BMI) and LV diastolic function [2], which represents the cornerstone of HFpEF. Another investigation reported that greater BMI and insulin resistance represented a higher risk of HFpEF compared to heart failure with reduced ejection fraction (HFrEF) [3]. Interestingly, the association of BMI with HFpEF versus HFrEF was more pronounced among women comparing to men [3].

In the last several years, the "obesity paradox" has drawn a lot of intention. A randomized controlled trial of 7599 patients with symptomatic HFpEF and HFrEF demonstrated that mortality risk gradually decreased with the increasing of BMI with a similar risk in the group with the highest BMI (> 35 kg/m^2) and those with BMI 30.0–34.9 kg/m^2 [4]. Another study that involved 108,927 patients with a decompensated HF analysis reported a strong negative correlation between BMI and in-

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hospital mortality, which resulted in a 10% reduction in mortality for every five-unit increase in BMI [5]. However, all investigations identified obesity using BMI and not body composition and the type of obesity. The pattern of regional adipose deposition could have significant adverse consequences beyond total body adiposity in obese patients with HFpEF [6]. The authors showed that intraabdominal fat was higher whereas epicardial fat was lower in patients with HFpEF [6].

This review article summarizes the current knowledge regarding mechanisms that explain the relationship between obesity and HFpEF, clinical trials and studies concerning this relationship, as well as the role of gender on the association between obesity and HFpEF, and the results of weight loss in these patients.

Pathophysiology

Obesity is strongly associated with other common non-cardiac clinical conditions such as systemic arterial hypertension, diabetes, metabolic syndrome, and obstructive sleep apnea, which could significantly contribute to HFpEF pathophysiology. Therefore, obesity may serve as a surrogate of these clinical conditions in the pathogenesis of HFpEF. Figure 1 shows the pathophysiological mechanisms that explain the association between obesity and HFpEF.

Obesity induces hemodynamic and biohumoral changes that are associated with functional and structural cardiac remodeling, which ultimately results in HFpEF development.

In obese subjects, excessive adipose accumulation is related to increased blood volume and reduced systemic vascular resistance, which results in augmentation of cardiac output [7, 8]. Fat-free mass in obese individuals is one of the most important factors in the development of a hypercirculatory state in obese patients. Considering the fact that heart rate is only slightly increased in obese subjects, the major reason for the increase of cardiac output in obesity lies in the increase of LV stroke volume.

Cardiac effort, and particularly LV effort in obese individuals, overcomes values predicted for those with normal body weight due to increased LV stroke work. LV end-diastolic pressure and pulmonary capillary wedge pressure are commonly elevated in moderate-to-severely obese patients.

According to the Frank–Starling law, which considers achieving force for the ejection of higher stroke volume by increased myofibers stretching, the initial phase of LV remodeling involves minor LV dilatation. In the second phase, the reduction of afterload has an important role that leads to LV dilatation and in the later phase to LV hypertrophy, which represents a compensatory mechanism to reduce wall stress and oxygen demand according to the law of LaPlace.

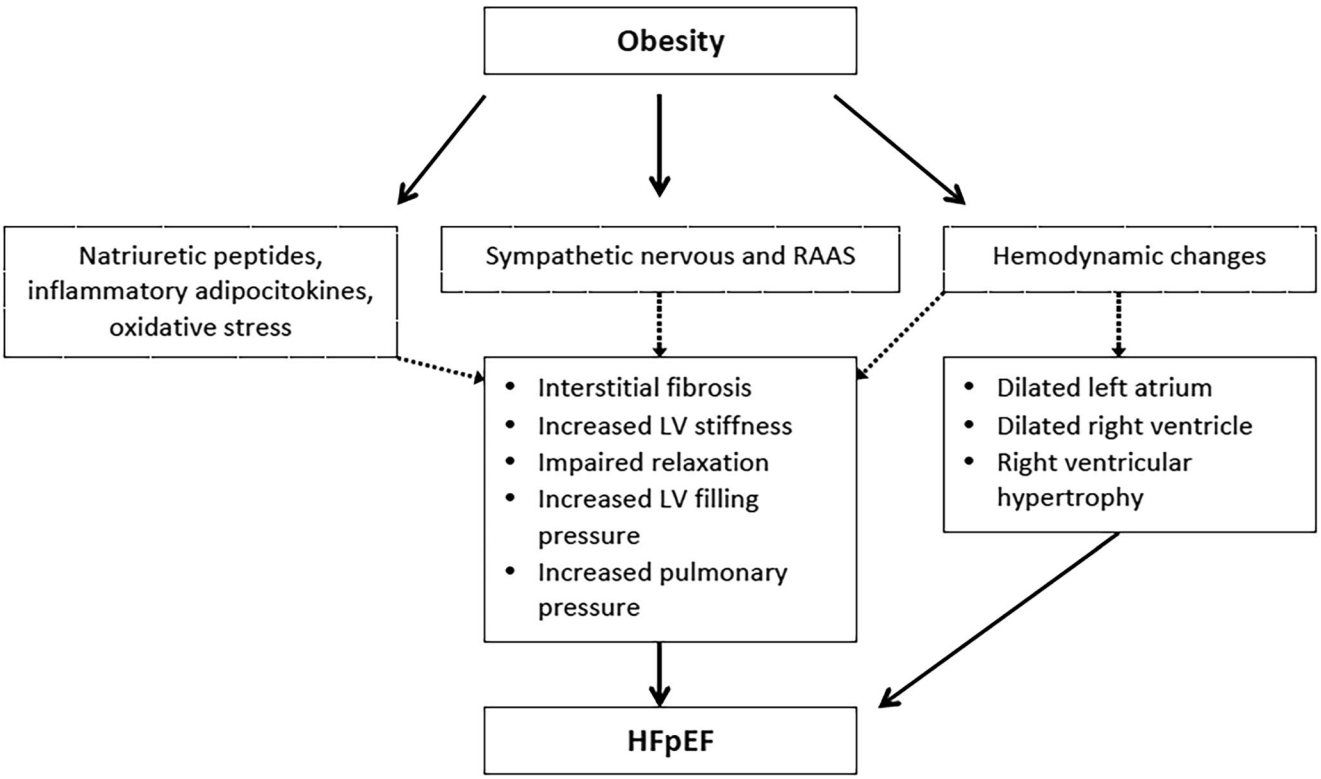

Fig. 1 Pathophysiology of the association between obesity and HFpEF. *HFpEF* heart failure with preserved ejection fraction, *RAAS* renin–angiotensin–aldosterone system

Pulmonary artery pressure is often, but not always elevated in obese persons. It could be increased because of LV failure, retrograde transmission of increased LV filling pressure over pulmonary veins to pulmonary circulation resulting in the raise of pulmonary vascular resistance in obese patients, and especially in patients with sleep apnea or obesity hypoventilation [9]. RV filling pressure is frequently increased in obese individuals, which further induces increased venous returns to the pulmonary circulation.

The Dallas Heart Study showed that visceral adipose tissue was related to lower cardiac output and higher systemic vascular resistance, whereas lower body subcutaneous fat was related to higher cardiac output and lower systemic vascular resistance [10]. Furthermore, the authors showed that abdominal subcutaneous fat was weakly associated with LV concentric remodeling in the general population. However, among the obese subjects, visceral adipose tissue, but not abdominal subcutaneous fat, was significantly associated with LV concentric remodeling [10].

A meta-analysis that included 4999 obese individuals and 6623 non-obese controls showed that the probability of having LV hypertrophy was much higher in obese than in non-obese subjects [11]. A meta-regression analysis showed a direct correlation between BMI and left-ventricular mass. Eccentric hypertrophy was more frequent than the concentric phenotype among obese patients with LV hypertrophy.

RV morphology and function are more difficult to assess in obese patients. Wong et al. showed that increased BMI is associated with decreased RV function in overweight and obese subjects without overt heart disease, even when independent of sleep apnea [12]. The MESA-Right Ventricle study reported that overweight or obese subjects had larger RV volume and RV mass than individuals with normal weight [13]. The authors partly explained the non-linear positive association between RV and BMI with the impact of sleeping breathing disorders on RV morphology.

Left atrial (LA) enlargement represents one of the cornerstone criteria for evaluation of LV diastolic function whose deterioration leads to HFpEF. Recently, Oliver et al. showed that LA dilatation was associated with BMI independently of race/ethnicity, blood pressure, LV mass, and N-terminal pro-brain natriuretic peptide [14]. This association was explained by the relationship between LA volume and visceral fat mass, but not with the association between LA volume and subcutaneous abdominal fat [14]. Other studies showed that not only LA volumes are increased in obese patients, but also function and mechanics, which deteriorates LV diastolic function and significantly contributes to HFpEF development [15].

Biohumoral changes in obesity consider activation of renin–angiotensin–aldosterone and the sympathetic nervous system, natriuretic peptide, inflammatory adipocitokines, and oxidative stress. All these mechanisms induce cardiac interstitial fibrosis that further increases cardiac rigidity and consequently elevates energy necessary for LV distension during diastole—an extremely energy-demanding process [8, 9]. Additionally, these biohumoral systems promote accelerated atherosclerosis, which also contributes to the development of HFpEF.

Observational studies and trials regarding obesity and HFpEF

A recently published study included 22,681 participants from four community-based cohorts and examined the incidence of HFpEF and HFrEF (ejection fraction > 50% vs. < 50%) during the median follow-up period of 12 years [3]. The authors demonstrated that greater BMI was associated with higher risk of HFpEF in comparison with HFrEF, and this relationship was more pronounced among women when compared with men [3]. Additionally, insulin resistance was associated only with HFpEF, but not HFrEF. Investigations regarding the impact of obesity on HFpEF occurrence or outcome in patients who already had diagnosed HFpEF is provided in Table 1.

Zhang et al. involved 96,424 patients from ten large studies with 59,263 HFpEF and 37,161 HFrEF. The authors found that increase in BMI was associated with all-cause mortality in the U-shaped with the nadir of risk at a BMI of 32–33 kg/m^2 [16]. Similar results were also obtained for the patients with HFrEF, and the relationship was also U-shaped but "flatter" than for HFpEF, with the nadir at a BMI of 33 kg/m^2 [16].

The data from the I-PRESERVE study showed that patients with BMI 26.5–30.9 kg/m^2 had the best outcome (death or cardiovascular hospitalization) and were used as a referent group [1]. The hazard ratio for the primary outcome was increased in the patients with BMI < 23.5 kg/m^2 and in those with BMI > 35 kg/m^2 in comparison with the referent group [1]. A similar association was revealed for all-cause mortality and hospitalization due to heart failure.

The TOPCAT trial demonstrated that the all-cause mortality risk was significantly higher in the patients with than in the ones without abdominal obesity [17]. The risk of both cardiovascular and non-cardiovascular mortality was also significantly higher in patients with abdominal obesity than in those without abdominal obesity [17].

Recently, Pandey et al. pooled the data from three different cohort studies (Women's Health Initiative, Multi-ethnic Study of Atherosclerosis and Cardiovascular Health Study) and showed that the dose–response relationship for BMI with HFpEF risk was more consistent than with HFrEF risk [18]. The authors showed that increase of BMI above the normal range (> 25 kg/m^2) was associated with a greater risk of HFpEF than HFrEF.

A study that included 42,170 postmenopausal women followed the participants for 13.2 years and found that obesity was associated with HFpEF but not with HFrEF development

Table 1 The association between obesity and HFpEF

Reference	Sample size	LVEF	Study type	Main findings
I-PRESERVE [1]	4109 patients	LVEF > 50%	Follow-up (49.5 months)	Patients with BMI 26.5–30.9 kg/m^2 had the best outcome (death or cardiovascular hospitalization)
Savji et al. [3]	22,681 participants	Unknown at baseline	Median follow-up of 12 years	Higher BMI was related with increased risk of HFpEF in comparison with HFrEF, and this relationship was more pronounced among women when compared with men
Zhang et al. [16]	96,424 patients (59,263 HFpEF and 37,161 HFrEF)	LVEF > 50% and LVEF < 50%	Meta-analysis	Increase in BMI was associated with all-cause mortality in U-shaped with the nadir of risk at a BMI of 32–33 kg/m^2
TOPCAT [17]	3310 patients with HFpEF	LVEF > 50%	Follow-up	The all-cause mortality was significantly higher in patients with abdominal obesity than in those without abdominal obesity.
Pandey et al. [18]	51,451 participants	Unknown at baseline	Data from three cohort studies	Dose–response relationship for BMI with HFpEF risk was more consistent than with HFrEF risk
Eaton et al. [19]	42,170 postmenopausal women	Unknown at baseline	13.2-year follow-up	Obesity was associated with HFpEF but not with HFrEF development. Obesity was a more powerful risk factor for HFpEF development among African American than in white women.

BMI body mass index, *HFpEF* heart failure with preserved ejection fraction, *HFrEF* heart failure with reduced ejection fraction, *LVEF* left ventricular ejection fraction

[19]. Obesity was a more powerful risk factor for HFpEF development among African American than in white women. In this study, the greatest risk for HFpEF development had hypertension (40.9%) and obesity (25.8%), with the highest population-attributable risk percentage found in African Americans.

Obesity paradox in HFpEF

Despite the negative relationship between BMI and cardiac remodeling, this association in HFpEF patients is specific and complicated. The obesity paradox refers to reduced risk profile in mildly overweight subjects in comparison with the individuals with normal and underweight which has been described in chronic HF. The studies regarding the obesity paradox on HFpEF are summarized in Table 2.

However, not all researches agree about the U-shaped relationship between BMI and mortality or risk for HFpEF development. Mohammed et al. showed that obesity was associated with better outcome adjusting for age, sex, and other concomitant comorbidities, and this relationship did not have a U-shape [24].

The I-PRESERVE trial showed that mildly overweight patients had the lowest rates of death or cardiovascular hospitalization [1]. Both underweight and severely overweight groups had higher rates of overall mortality than mild overweight patients.

Ather et al. reported that the absence of obesity was an independent predictor of mortality in both, HFpEF and HFrEF patients [20]. Although obesity decreased mortality risk in HFpEF more than in HFrEF subjects, there was no statistical significance between these two groups [20].

Recently published results from the large registry revealed that higher BMI was associated with lower 30-day mortality, up to 30 kg/m^2 with a small risk increase above 30 kg/m^2 among subjects with HFpEF [21]. A modest relationship was observed in HFrEF subjects, with no risk increase above 30 kg/m^2. This study indicated that the obesity paradox for 30-day mortality exists in HFrEF, but not in the patients with HFpEF. The differential slope of obesity and mortality among HFpEF and HFrEF patients potentially suggests differing mechanistic factors, requiring further exploration.

A community-based study showed again that the lack of obesity was associated with increased overall mortality risk during the follow-up period of 31 months in both HFpEF and HFrEF patients [22]. There was no difference in the mortality risk between these two groups of patients.

A subanalysis of the MAGGIC meta-analysis involved 23,967 subjects and reported that mortality risk had a U-shaped form in both HFpEF and HFrEF patients with highly positioned nadir at 30.0–34.9 kg/m^2 [23].

Table 2 The association between obesity paradox and HFpEF

Reference	Sample size	LVEF	Study type	Main findings
I-PRESERVE [1]	4109 patients	LVEF > 50%	Follow-up (49.5 months)	Mildly overweight patients had the lowest rates of death or cardiovascular hospitalization. Underweight and severely overweight groups had higher mortality rates than mildly overweight.
Ather et al. [20]	2843 patients with HFpEF and 6599 with HFrEF	LVEF > 50% and LVEF < 50%	2-year follow-up	The absence of obesity was the independent predictor of mortality in both HFpEF and HFrEF patients.
Powell-Wiley et al. [21]	39,647 patients with HFpEF and HFrEF	LVEF > 50% and LVEF < 50%	30-day and 1-year follow-up	The obesity paradox for 30-day mortality exists at all BMI levels in HFrEF but not in patients with HfpEF
Iorio et al. [22]	2314 patients (941 HFrEF and 1373 HFpEF)	LVEF > 50% and LVEF < 50%	31-month follow-up	The lack of obesity was associated with increased overall mortality in both groups (HFpEF and HFrEF), and there was no difference in mortality rate between these groups.
Padwal et al. [23]	23,967 subjects	LVEF > 50% and LVEF < 50%	MAGGIC meta-analysis (3-year follow-up)	U-shaped form in both HFpEF and HFrEF patients with highly positioned nadir at 30.0–34.9 kg/m^2.

BMI body mass index, *HFpEF* heart failure with preserved ejection fraction, *HFrEF* heart failure with reduced ejection fraction, *LVEF* left ventricular ejection fraction

There are several hypotheses that might explain the obesity paradox. One of them suggested that adiponectin, an adipocyte-specific cytokine, inversely associated with BMI in subjects with heart failure [25]. Furthermore, lower adiponectin levels are associated with increased mortality, which means that patients with increased BMI have higher adiponectin and lower mortality. The other mechanisms of obesity paradox include anti-inflammatory effects of elevated lipoproteins and decreased response of renin–angiotensin–aldosterone system.

The influence of gender on the association between obesity and HFpEF

The large study that included more than 110,000 patients hospitalized due to HF showed that 63% of HFpEF subjects occurred in women compared with 47% of HF with mildly reduced EF cases and 36% of HFrEF patients [26]. This study showed that HFpEF is more prevalent in women compared with men; however, incidence rates of HFpEF were similar between sexes, and HFpEF was the most common subtype of HF in women [26].

The most important pathophysiological mechanisms that could explain more prevalent HFpEF among women are alterations in ventricular–vascular stiffness [27], LV hypertrophy, and smaller LV cavity size [28]. These changes predispose women to diastolic dysfunction and further to HFpEF.

Obesity is more important risk factor for HFpEF development in women than in men [3, 29]. Savji et al. followed 22,681 subjects for 12 years and reported that obesity was related with a higher risk of HFpEF than of HFrEF and this effect was more prominent in women than in men [3]. The authors showed that obesity was a major risk factor for HFpEF but not for HFrEF in women. This suggests that obesity has a different sex-related effect on various HF types.

The incidence of obesity-related HFpEF in women could only increase due to the epidemic of obesity and metabolic syndrome nowadays, which is why physicians should be particularly careful on obese women in order to timely diagnose HFpEF.

Clinical implications—weight loss and physical activity

Many of the hemodynamic and cardiac alterations associated with obesity are reversible with significant weight reduction. Our previous meta-analyses showed significant improvement in left and right ventricular structure and function after bariatric surgery [30, 31]. Voluntary weight reduction can be achieved by diet with or without exercise. However, data

regarding the influence of weight loss and physical activity on HFpEF are limited.

A recently published study that involved a limited number of patients showed that surgery-induced weight loss in women with HFpEF and obesity was related to improved symptoms, reverse cardiac remodeling, and improved myocardial relaxation during diastole [32].

McDowell et al. in the systematic review reported that intentional weight loss can improve New York Heart Association classification, quality of life, and exercise capacity in patients with HF [33]. A study that involved 51,451 patients reported that increased physical activity was related to reduced risk of HFpEF independently of BMI [18]. Wohlfahrt et al. revealed that weight gain was associated with elevated LV diastolic stiffness over 4 years of follow-up, which could be an important factor for HFpEF development [34].

Kitzman et al. recently published a very important work on this topic and for the first time showed benefits of weight reduction and exercise in obese patients with HFpEF [35]. The authors included 100 patients with HFpEF and BMI > 30 kg/m^2 who were randomized to 20 weeks of diet ($n = 24$), exercise ($n = 26$), both ($n = 25$), and control group ($n = 25$). Both exercise and diet modifications were related to improved physical capacity (increased peak oxygen consumption), and the combination had the best effect. Body weight loss was associated with the improvement in NYHA functional class. Dietary intervention was associated with the decrease in LV mass, LV wall thickness, and improvement in diastolic dysfunction [35].

Conclusion

Obesity represents a very common comorbidity in the patients with HFpEF. However, it seems that obesity is not only comorbidity, but also an important risk factor for HFpEF development because it is associated with adverse hemodynamic effects and cardiac remodeling. The investigations showed that central adiposity is associated with greater risk for HFpEF development than peripheral adiposity. There is a lack of agreement regarding the obesity paradox on cardiac remodeling and the risk of HFpEF. On the other hand, there is an agreement that weight loss and physical activity have great benefits on cardiac structure and function, as well as on improvement of functional capacity. Considering the fact that pharmacological studies were mostly unsatisfactory in the patients with HFpEF, a different approach is obviously necessary and weight reduction appears as a good alternative until the medical approach provides better outcome in this population of patient. Further studies are necessary to identify the pharmacologic approach and possible interventions that could enable better outcome and improved quality of life in obese patients with HFpEF.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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