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HYPERTENSION AND OBESITY (E REISIN, SECTION EDITOR)

Weight Reduction for Obesity-Induced Heart Failure with Preserved Ejection Fraction

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Abstract

Purpose of Review Heart failure with preserved ejection fraction mainly affects the elderly. The obesity phenotype of heart failure with preserved ejection fraction reflects the coexistence of two highly prevalent conditions in the elderly. Obesity may also lead to heart failure with preserved ejection fraction in middle-aged persons, especially in African American women.

Recent Findings Obesity is twice as common in middle-aged than in elderly persons with heart failure with preserved ejection fraction. Obese middle-aged persons with heart failure with preserved ejection fraction are less likely to be Caucasian and to have atrial fibrillation or chronic kidney disease as comorbidities than elderly patients with heart failure with preserved ejection fraction. Obesity-associated low-grade systemic inflammation may induce/heighten inflammatory activation of the coronary microvascular endothelium, leading to cardiomyocyte hypertrophy/ stiffness, myocardial fibrosis, and left ventricular diastolic dysfunction.

Summary Both substantial weight reduction with bariatric surgery and lesser levels of weight reduction with caloric restriction are promising therapeutic approaches to obesity-induced heart failure with preserved ejection fraction.

Keywords Obesity · Heart failure with preserved ejection fraction · Adipose tissue · Bariatric surgery · Caloric restriction

Introduction

The obesity epidemic is leveling off in men but continues to progress in women [1]. Furthermore, the prevalence of morbid obesity (body mass index [BMI] ≥ 40 kg/m^2) is growing at a faster rate than that of obesity as a whole [2]. Obesity and morbid obesity are associated with changes in left ventricular (LV) structure and function, most commonly concentric remodeling and diastolic dysfunction [3–6]. LV concentric remodeling and diastolic dysfunction (LVDD) are the underpinnings of heart failure with preserved ejection fraction (HFpEF). A likely corollary of the obesity epidemic is the increasing incidence of HFpEF, particularly in women and African Americans [7, 8••, 9]. We review how obesity, female sex, and African American ethnicity may affect the incidence and outcome of HFpEF. We then consider how obesity fosters the development of HFpEF and surgical versus non-surgical approaches to weight reduction.

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Obesity and Heart Failure with Preserved Ejection Fraction

Increases in BMI and waist circumference (WC) are associated with increased risk of heart failure (HF). The relative risk of HF incidence is 1.41 for each 5 kg/m^2 increment in BMI and 1.29 for each 10 cm increase in WC [10]. The cumulative burden of increasing BMI and blood pressure (BP) from childhood to adulthood is associated with the development of LV hypertrophy (LVH), and the association is stronger for BMI than BP [11]. Young obese women who are otherwise healthy have a greater LV mass and relative wall thickness than non-obese women [12]. After adjustment for age, systolic BP, and type 2 diabetes (T2D), LV mass/height$^{2.7}$ and LV mass/fat-free mass ratio are greater in obese women than in obese men

[13]. The association between obesity and LVDD was first reported 15 years ago [14]. High BMI correlated with greater LV mass, wall thickness, and filling pressure and not with LV ejection fraction (LVEF) in patients free of obstructive coronary artery disease (CAD) [14]. High BMI also increases the risk of LVDD in metabolically healthy obese women free from dyslipidemia, HTN, and T2D [15]. Obesity confers a particularly high risk of HFpEF in women and is more closely associated with the incidence of HFpEF than HF with reduced ejection fraction (HFrEF) in both sexes [8••]. The attributable risk of HFpEF is estimated to range from 44 to 49% when BMI is ≥ 27.5 kg/m^2 and WC > 100 cm in men and $>$ 94 cm in women [16]. Of major pathogenic importance, the association between BMI and LVDD is independent of confounding risk factors. Increased BMI was associated with worse LVDD independent of LVH, HTN, T2D, and obstructive sleep apnea (OSA) in 950 participants in the Cardiovascular Abnormalities and Brain Lesions study [17].

Sex and Heart Failure with Preserved Ejection Fraction

Nearly two-thirds of the 40,354 Americans hospitalized for HFpEF from 2005 to 2010 were elderly women with a mean age of 78 years [18]. More recently, 55% of 9957 patients enrolled in the Swedish Heart Failure registry for HFpEF were elderly women (mean age 79 years) [19••]. Women have smaller LV dimensions after adjustment for height than men [20]. Obese women have greater LV mass/height$^{2.7}$ and LV mass/fat-free mass ratios than non-obese women after adjustment for age, systolic BP, and T2D [13]. The increase in LVDD in women compared with men was unrelated to differences in systolic arterial-ventricular coupling in the prospective comparison of angiotensin receptor neprilysin inhibition (ARNI) with angiotensin receptor blockade (ARB) on the management of Heart FailUre with preserved ejectiOn fracTion (Paramount) trial [21]. However, not all investigators have found that women are at greater risk of developing HFpEF than men [22, 23]. After adjustment for age, BP, BMI, antihypertensive treatment, and previous myocardial infarction, women and men have been shown to be at similar risk for HFpEF [24]. Despite conflicting data, HFpEF is generally believed to be more prevalent, with a nearly twofold greater prevalence, in women than in men [25]. The 2018 statistical report from the American Heart Association indicates that HFpEF is the most common form of HF in women, has a similar incidence in women and men, but is more prevalent in women as they live longer than men [26].

African Americans and Heart Failure with Preserved Ejection Fraction

LV mass and incidence of LVH are significantly greater in African Americans than in Caucasians after adjustment for fat mass, fat-free mass, systolic BP, age, and socioeconomic status [27]. The greater impairment in microvascular endothelial function and increases in arterial wave reflection and stiffness in African Americans compared with Caucasians likely contribute to the higher prevalence of LVH in African Americans [28]. Furthermore, the prevalence of obesity in general and morbid obesity in particular is high in African Americans, reaching 54 and 52.9%, respectively, in patients enrolled in the Jackson Heart Study from 2000 to 2013 [29]. Morbid obesity is particularly more severe in African American than in Caucasian women [30].

The most common form of HF was HFpEF in middle-aged African Americans who, enrolled in the Jackson Mississippi cohort of Atherosclerosis Risk in Communities (ARIC) study, underwent echocardiography in 1993–1995 and were followed for 13.7 years [9]. Obesity was a greater risk for HFpEF in African American than in Caucasian women after adjustment for HTN and T2D in a multi-racial cohort of 42,170 postmenopausal women [31]. However, African Americans and Caucasians had an equal lifetime risk of HFpEF in 2 large prospective cohorts: The cardiovascular health study (CHS) and the multi-ethnic study of atherosclerosis (MESA) [22]. It is important to note that both African American men and women are generally under-represented in multi-racial clinical studies. The percentage of African Americans enrolled is commonly $< 20\%$ in multi-racial studies, even when they are conducted in states where African Americans represent $\geq 40\%$ of the population [32, 33]. Thus, whether the abovementioned multi-racial studies accurately capture the clinical profile of HFpEF in African Americans remains to be determined.

Data regarding HFpEF outcomes in African Americans are also controversial. Observational studies indicate that African Americans have worse outcomes than Caucasians [32, 33]. African Americans had a significantly higher 5-year mortality than Caucasians after adjustment for known risk factors in the cohort of 3303 HFpEF patients from the Duke Cardiovascular Databank [32]. However, analysis of administrative data (nationwide inpatient sample and Medicare) does not support an outcome difference between African Americans and Caucasians with HF/HFpEF [34, 35]. Administrative data are valuable for evaluation of adherence to guidelines and collection of clinical information after hospitalizations, but may be less useful for assessing the clinical course of chronic conditions.

Pathogenesis of Obesity-Induced Heart Failure with Preserved Ejection Fraction

As obesity progresses, visceral adipose tissue (VAT) accumulates, becomes inflamed, and results in low-grade systemic

inflammation. Low-grade systemic inflammation then activates inflammatory processes in the coronary microvascular endothelium, leading to impaired cardiomyocyte relaxation, increased myocardial stiffness, and LVDD [36, 37••].

Accumulation of Visceral Adipose Tissue

VAT refers to the intra-abdominal accumulation of mesenteric and omental AT [38]. An enlarged WC clinically signals an increased VAT mass [39]. In the Dallas Heart Study, VAT mass, measured by magnetic resonance imaging (MRI) at the L2-L3 intervertebral level, was associated with LV concentric remodeling [40]. The association between VAT and LV concentric remodeling is independent of age, sex, ethnicity, and obesity status and is stronger in women than in men [41, 42]. Eleven-year follow-up of 1806 MESA participants revealed that VAT and not subcutaneous AT (SAT) mass was independently associated with hospitalization for incident HFpEF [43]. In the Treatment Of Preserved CArdiac function Heart Failure with an aldosterone antagonist (TOPCAT) Trial, men with WC ≥ 102 cm and women with WC ≥ 88 cm were at higher risk of all-cause mortality than patients with normal range WC [44••]. The association of central obesity with fatal outcomes in HFpEF points to a major role for VAT in the pathogenesis of HFpEF.

Visceral Adipose Tissue and Low-Grade Systemic Inflammation

Accumulation of VAT over time leads to VAT inflammation and low-grade systemic inflammation, as evidenced by elevated plasma levels of C-reactive protein (CRP), interleukin (IL)-6, and tumor necrosis factor (TNF)-α [45–47]. The association between the amount of VAT and elevated markers of inflammation is independent of other measures of obesity [48]. Accumulation of VAT initially results in an anti-inflammatory response with the release of adipokines and the recruitment of alternatively activated macrophages (M2) that facilitates VAT expansion [49, 50]. Continued adipocyte hypertrophy leads to leptin release, monocyte chemotactic protein 1 (MCP 1) expression, mechanical stress, hypoxia, and cell death, with production of pro-inflammatory adipokines that promote proliferation and AT infiltration of classically activated macrophages (M1) [50–53]. Circulating markers of inflammation like CRP and IL-6 do not reliably reflect the degree of VAT inflammation or low-grade systemic inflammation. CRP correlates more closely with SAT than with VAT, and only 30% of IL-6 originates from AT [54]. Truncal fat contributes to higher CRP in women than in men [54, 55]. Profiling circulatory cytokines may help assess VAT-related systemic inflammation and metabolic health in obese African American women [56].

Coronary Microvascular Inflammation

Inflammatory activation of the coronary microvascular endothelium leads to reduced cardiomyocyte elasticity/function and increased myocardial stiffness/fibrosis through the activation of two signaling pathways [37••]. In the first pathway, endothelial expression of adhesion molecules enables infiltration of inflammatory cells, uncouples endothelial nitric oxide synthase {eNOS), reduces NO bioavailability and decreases soluble guanylate cyclase (sGC) stimulation, thereby reducing the activity of cyclic guanosine monophosphate (cGMP) and protein kinase G (PKG) [37••, 57]. Low PKG activity promotes cardiomyocyte hypertrophy and titin hypophosphorylation that increase passive LV stiffness (Fig. 1) [36]. The second pathway targets suppression of the unfolded protein response that may lead to interstitial accumulation of destabilized proteins [58]. Microvascular endothelial inflammation is associated with increased expression of inducible NOS (iNOS) and reduces the activity of proteins involved in the unfolding response [58]. In addition to activation of these signaling pathways, coronary microvascular rarefaction and a Sirtuin (SIRT) 3–dependent defect in endothelial cell metabolic programming and angiogenesis may affect the progression of perivascular and myocardial fibrosis in HFpEF [59–61].

Obese Phenotypes of Heart Failure with Preserved Ejection Fraction

Obesity and HFpEF are extremely prevalent conditions. As the prevalence of both obesity and HFpEF continues to rise, the two conditions are increasingly likely to coexist in elderly patients, especially in post-menopausal women [7, 62, 63••]. The average BMI of patients in the Irbesartan in heart failure with PRESERVEd ejection fraction (I-PRESERVE) trial was 29.6 kg/m^{2,}, with 41.4% of participants having a BMI > 30 kg/m^2 [64]. The average age in I-PRESERVE was 71.6 years, and 29.4% of participants were older than 75 years. The mean age of patients hospitalized for HFpEF from 2005 to 2010 was 78 years, and the mean age of women with HFpEF in the recent Swedish HF registry is 79 years [18, 19••].

Obesity and Heart Failure with Preserved Ejection Fraction in Elderly Patients

Obesity has been shown to increase height-adjusted right ventricle (RV) dimensions in women with increased RV ejection fractions and in men with increased RV volumes [65]. Extremely obese patients are more likely to develop impaired systolic and diastolic cardiac function and pulmonary hypertension [66]. RV prominence, interventricular interaction and increased systemic inflammation characterize the coexistence

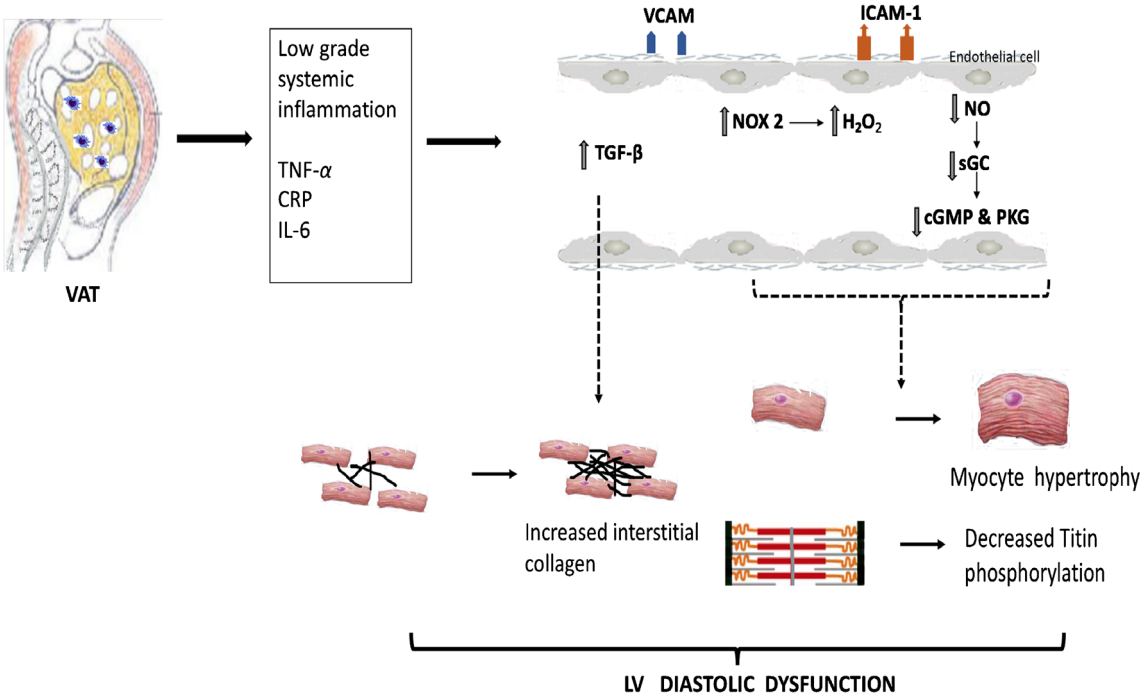

Fig. 1 As obesity progresses, visceral adipose tissue (VAT) inflammation promotes low-grade systemic inflammation as evidenced by elevated plasma levels of C-reactive protein (CRP), interleukin (IL)-6, and tumor necrosis factor (TNF)-α. Systemic inflammation induces/heightens inflammatory activation of the coronary microvascular endothelium with increased expression of vascular cell adhesion molecule (VCAM) and intracellular adhesion molecule (ICAM-1). Enhanced release of transforming growth factor (TGF)-β by monocytes promotes conversion of fibroblasts to myofibroblasts and myocardial deposition of collagen. Increased macrophage expression of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase2 (NOX2) stimulates production of hydrogen peroxide (H_2O_2). Decreased nitric oxide (NO) bioavailability and oxidative stress reduce soluble guanylate cyclase (sGC) stimulation, thereby lowering cyclic guanosine monophosphate (cGMP) and protein kinase G (PKG) activity. Low PKG activity leads to cardiomyocyte hypertrophy and titin hypo-phosphorylation that, with increased interstitial myocardial collagen deposition, impairs LV relaxation and increases LV stiffness

of obesity and HFpEF i.e. the obese phenotype of HFpEF in the elderly [67, 68].

Obesity and Heart Failure with Preserved Ejection Fraction in Middle-Aged Patients

The prevalence of obesity was much greater in middle-aged (age < 55 years) than in older (age ≥ 75 years) HFpEF patients in the multinational registry of Asian patients with HF (ASIAN-HF): 36 versus 16% [69••]. Middle-aged patients with HFpEF were more likely to be obese and less likely to be Caucasian in the Candesartan Cilexetil in heart failure assessment and reduction of mortality and morbidity (CHARM Preserved), TOPCAT, and in I-PRESERVE trials [70••]. In the USA, African Americans have a high prevalence of obesity [30, 71]. The prevalence of obesity was 59% in African American women versus 41% in women of other ethnic backgrounds in the New York HFpEF registry [72]. The clinical characteristics of patients with HFpEF were similar in the Urban Baltimore community, with a prevalence of 84% in women and 76% in African Americans and a mean BMI of 37 kg/m^2 [73]. HFpEF most often occurs in elderly patients who have multiple comorbidities, particularly atrial fibrillation and chronic kidney disease that contribute to functional impairment [74]. Middle-aged patients with HFpEF have fewer comorbidities and are twice as likely to be obese than elderly patients with HFpEF [69••, 70••]. The consistent association of middle age and obesity with HFpEF in 11 Asian regions and in the USA suggests that obesity hastens the development of HFpEF; i.e., there is an obesity-induced phenotype of HFpEF.

Weight Reduction in Obesity-Induced Heart Failure with Preserved Ejection Fraction

To establish the central role of obesity in the pathobiology of HFpEF in middle-aged patients, it will be necessary to demonstrate improvement/reversal of LVDD and increased functional capacity after substantial weight loss. Bariatric surgery is the most reliable intervention for weight loss. It is approved by the FDA for the treatment of patients with BMI ≥ 40 kg/m^2 or ≥ 35 kg/m^2 with an obesity-associated comorbidity. The mean age of patients undergoing bariatric surgery is 46 years, and recent data indicate that, while associated with a moderate increase in the risk of complications, bariatric surgery is a safe surgical procedure in elderly patients [75]. However, elderly patients lose less weight than middle-aged patients after bariatric surgery. In patients unwilling to undergo an invasive

procedure, mild weight reduction with caloric restriction (CR) is a promising approach.

Bariatric Surgery

Bariatric surgery significantly reduces incident HF (HFpEF and HFrEF) in morbidly obese patients [76–78]. Combined analysis of data from the Swedish registry of patients treated with intensive lifestyle interventions and the Scandinavian obesity surgery registry showed that gastric bypass (GB) surgery decreases HF incidence by 50% more than lifestyle management [77]. Since obesity is a major risk factor for HF and diet, exercise and pharmacotherapy are relatively ineffective for weight loss, bariatric surgery is now considered to be the treatment of choice for obese HFrEF patients who are resistant to guideline-directed medical therapy for their HFrEF and may become eligible for cardiac transplantation after substantial weight loss [79, 80]. Bariatric surgery may be even more beneficial for the treatment of HFpEF than HFrEF. Weight loss, either dietary or surgical, markedly decreases LV mass in obese patients with LV concentric remodeling and preserved EF [81–83]. The effects of bariatric surgery on LV structure and function are most commonly assessed by 2D-Doppler echocardiography [84]. Trans-mitral valve pulmonary veins and tissue Doppler of LV diastolic function including septal and lateral mitral annular velocities and LV diastolic strain all improve after bariatric surgery [85–88]. LV mass index (LVMI, indexed to height) decreased from 44.0 to 38.4 g/m$^{2.7}$ ($p < 0.01$) after GB surgery in 354 patients with morbid obesity but did not change in 249 counterparts who sought bariatric surgery but could not afford it [89]. Two meta-analyses confirmed that bariatric surgery reduces LV mass, improves LVDD, and reduces left atrial size in patients with LV concentric remodeling and preserved EF [90, 91]. Of note, bariatric surgery reduces LVMI independent of obesity-related co-morbidities like OSA [92]. Furthermore, LVMI continues to decline at a linear rate for 24 months after bariatric surgery, while rates of weight loss and loss of lean mass and fat mass plateau at 9 months [93]. In addition to reversing LV concentric remodeling, GB surgery has been shown to improve quality of life and functional capacity in patients with HFpEF, as evidenced by a lower score on Minnesota living with HF questionnaire and an improved NYHA functional class [94].

Bariatric surgery consistently reduces the amount of VAT by 40–70% in obese patients [95–99]. VAT begins to decrease as early as 1 month after surgery and continues to decrease for 24 months, then stabilizes [96, 99]. Bariatric surgery reduces VAT mass to a greater extent in women than men [100]. The effects of Roux-en-Y GB surgery on circulating markers of inflammation have been well studied. Blood levels of CRP and IL-6 are consistently lower after GB surgery, while TNF-α levels are lower or unchanged [101–105]. Sleeve gastrectomy and GB surgery may have similar effects on CRP, IL-6, and TNF-α levels [104, 106]. Two meta-analyses have measured inflammatory markers after bariatric surgery [107, 108]. The first showed that levels of CRP and IL-6 were significantly lower after bariatric surgery, while the change in TNF-α did not reach statistical significance. In the second meta-analysis, CRP, IL-6, and TNF-α levels decreased significantly after bariatric surgery. Thus, bariatric surgery appears to be a reliable intervention to reduce both VAT mass and circulating markers of inflammation.

Caloric Restriction

Moderate weight reduction is associated with a metabolic adaptation that may attenuate low-grade systemic inflammation and reduce inflammation in the coronary microvascular endothelium. Reduced inflammation in the coronary microvasculature may alleviate LVDD and improve the functional capacity of HFpEF patients.

Caloric restriction (CR) is a dietary intervention that aims at a 25% reduction of metabolic requirements from baseline values [109]. The Comprehensive Assessment of the Long-term Effects of Reducing Intake of Energy (CALERIE 1) study showed that 6 months of CR decreased body weight by 10 (0.8)% in overweight, healthy, sedentary middle-aged men, and pre-menopausal women [109]. CR appears to induce metabolic adaptation as the decrease in energy expenditure exceeds that expected from the loss of fat-free mass. The CALERIE 2 study investigated the effects of CR for 2 years on BP, CRP, plasma lipids, fasting insulin, and insulin resistance in young and middle-aged (21–51 years) healthy non-obese (BMI 22.0–27.5 kg/m^2) men and women. The mean caloric intake and weight reduction were − 11.9% and − 7.5 kg respectively at 2 years. All conventional cardiometabolic risk factors were reduced at 2 years after controlling for relative weight loss [110••]. Two years of CR at levels achieved in CALERIE 2 is well tolerated and safe providing close monitoring of bone loss and red blood cells [111]. An ancillary study of CALERIE 2 confirmed that CR for 2 years induces metabolic adaptation and reduces thyroid axis activity and reactive oxygen species production in 34 non-obese middle-aged healthy men and women [112••]. Another ancillary study of CALERIE 2 showed that, in addition to reductions in BP, total cholesterol, and cardiovascular risk, a 9% reduction on body weight is associated with a significant decrease in VAT mass at 12 and 24 months in non-obese middle-aged healthy men and women [113]. The Calorie Restriction in Overweight SeniorS: Response of Older Adults to a Dieting Study (CROSSROADS) trial randomized elderly (age > 65 years) and obese (BMI 30–40 kg/m^2) patients who were receiving at ≥ 1 medication for HTN, T2D, or dyslipidemia, to CR, exercise, or diet modification for 6 months [114]. Per protocol, the body weight of patients randomized to exercise

and dietary modification was to be kept constant. Patients randomized to CR lost 4.1% of body weight and no VAT mass. However, exercise that has been reported to decrease VAT mass by 6.1% in the absence of change in body weight did not alter VAT mass in CROSSROADS [115, 116]. Observational data suggest that CR for several years may slow down age-related deterioration in LV diastolic function [117]. Twenty weeks of CR and CR plus exercise training resulted in moderate improvement in peak aerobic capacity but did not enhance the quality of life in obese elderly patients with HFpEF [118].

In summary, the pathobiology and treatment of the obese phenotype of HFpEF may differ in middle-aged and elderly patients. In the elderly, obesity and HFpEF are not closely related and bariatric surgery and CR are unlikely to improve LVDD and HFpEF, although bariatric surgery is likely to improve patients' sense of well-being and cardiovascular disease risk. In the middle-aged, bariatric surgery and possibly CR may improve LVDD and HFpEF. Thus, treatment needs to focus on weight reduction in middle-aged patients with obesity-induced HFpEF.

Compliance with Ethical Standards

Conflict of Interest The authors declare no conflicts of interest relevant to this manuscript.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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