Published in final edited form as:

Circulation. 2017 July 04; 136(1): 6–19. doi:10.1161/CIRCULATIONAHA.116.026807.

Evidence Supporting the Existence of a Distinct Obese Phenotype of Heart Failure with Preserved Ejection Fraction

Masaru Obokata, MD, PhD¹, Yogesh N. V. Reddy, MD¹, Sorin V. Pislaru, MD, PhD¹, Vojtech Melenovsky, MD, PhD^{1,2}, and Barry A. Borlaug, MD¹

¹The Department of Cardiovascular Medicine, Mayo Clinic Rochester, MN 55906

²Institute for Clinical and Experimental Medicine – IKEM, Prague, Czech Republic

Abstract

Background—Heart failure (HF) with preserved ejection fraction (HFpEF) is a heterogeneous syndrome. Phenotyping patients into pathophysiologically homogenous groups may enable better targeting of treatment. Obesity is common in HFpEF and has many cardiovascular effects, suggesting it may be a viable candidate for phenotyping. We compared cardiovascular structure, function, and reserve capacity in subjects with obese HFpEF, non-obese HFpEF, and controls.

Methods—Subjects with obese HFpEF (BMI ≥ 35 kg/m², n=99), non-obese HFpEF (BMI <30 kg/m², n=96), and non-obese controls free of HF (n=71) underwent detailed clinical assessment, echocardiography and invasive hemodynamic exercise testing.

Results—Compared to both non-obese HFpEF and controls, subjects with obese HFpEF displayed increased plasma volume (3907 [3563,4333] vs. 2772 [2555,3133] and 2680 [2380,3006] ml, $p<0.0001$), more concentric left ventricular remodeling, greater right ventricular dilatation (base 34 ± 7 vs. 31 ± 6 and 30 ± 6 mm, $p=0.0005$; length 66 ± 7 vs. 61 ± 7 and 61 ± 7 mm, $p<0.0001$), more right ventricular dysfunction, increased epicardial fat thickness (10 ± 2 vs. 7 ± 2 and 6 ± 2 mm, $p<0.0001$), and greater total epicardial heart volume (945 [831,1105] vs. 797 [643,979] and 632 [517,768] ml, $p<0.0001$), despite lower NT-proBNP levels. Pulmonary capillary wedge pressure was correlated with body mass and plasma volume in obese HFpEF ($r=0.22$ and 0.27 , both $p<0.05$), but not in non-obese HFpEF ($p=0.3$). The increase in heart volumes in obese HFpEF was associated with greater pericardial restraint and heightened ventricular interdependence, reflected by increased ratio of right to left heart filling pressures (0.64 ± 0.17 vs. 0.56 ± 0.19 and 0.53 ± 0.20 , $p=0.0004$), higher pulmonary venous pressure relative to left ventricular transmural pressure, and greater left ventricular eccentricity index (1.10 ± 0.19 vs. 0.99 ± 0.06 and 0.97 ± 0.12 , $p<0.0001$). Interdependence was enhanced as pulmonary artery pressure load increased (interaction $p<0.05$). As compared to non-obese HFpEF and controls, obese HFpEF subjects displayed worse exercise capacity (peak oxygen consumption 7.7 ± 2.3 vs. 10.0 ± 3.4 and 12.9 ± 4.0 ml/min*kg, $p<0.0001$), higher biventricular filling pressures with exercise and depressed pulmonary artery vasodilator reserve.

Address for correspondence: Barry A. Borlaug, MD, Mayo Clinic and Foundation, 200 First Street SW, Rochester, MN 55905, Phone: 507-255-1051, Fax: 507-266-0228, borlaug.barry@mayo.edu.

Disclosures
None.

Conclusions—Obesity-related HFpEF is a genuine form of cardiac failure and a clinically relevant phenotype that may require specific treatments.

Keywords

HFpEF; obesity; pulmonary hypertension; pericardium; epicardial fat

INTRODUCTION

Approximately one-half of patients with heart failure (HF) have a preserved ejection fraction (HFpEF). The pathophysiology of HFpEF is complex, and this disorder has been increasingly characterized as a heterogeneous syndrome that is caused or exacerbated by a variety of comorbidities linked to both cardiac and extracardiac abnormalities.^{1, 2} Clinical trials to date have not identified a treatment that improves prognosis of people with HFpEF, but phenotyping patients into pathophysiologically homogenous groups has been recently hypothesized as a means of better targeting of treatments moving forward.^{1, 2}

Obesity has reached epidemic proportions worldwide and is a common finding in people with HFpEF.^{1–3} Obesity has many deleterious effects on the cardiovascular system, mediated by changes in volume status, cardiac loading, energy substrate utilization, tissue metabolism and systemic inflammation that are believed to promote disease progression.^{4–6} This led us to hypothesize that obesity-related HFpEF may represent a clinically-relevant phenotype within the broader spectrum of HFpEF. To explore this hypothesis, we performed a detailed characterization of cardiovascular structure, function and reserve capacity in subjects with HFpEF and class II or greater obesity as compared with non-obese HFpEF and non-HF controls.

METHODS

Study Population

Consecutive subjects with HFpEF undergoing invasive hemodynamic exercise testing at the Mayo Clinic catheterization laboratory between 2000 and 2014 were retrospectively identified. HFpEF was defined by clinical symptoms of HF (exertional dyspnea, fatigue), EF $\geq 50\%$, and directly measured elevation in left heart filling pressures (pulmonary capillary wedge pressure, PCWP) at rest ($>15\text{mmHg}$) and/or with exercise ($>25\text{mmHg}$). Subjects with reduced EF (EF $<50\%$), isolated right-sided HF, valvular heart disease ($>$ moderate left-sided regurgitation, $>$ mild stenosis), unstable coronary disease or recent revascularization, constrictive pericarditis, high output HF, or cardiomyopathy were excluded.

In order to investigate the characteristics of obesity in HFpEF, we categorized participants according to body mass index (BMI). Non-obese HFpEF was defined by BMI $<30\text{kg/m}^2$ and obese HFpEF was defined by the presence of class II or greater obesity (BMI $\geq 35\text{kg/m}^2$). We excluded patients with class I obesity (BMI 30–34.9) in order to maximize phenotypic differences associated with greater body mass. As a separate control, we also compared obese and non-obese HFpEF subjects to non-obese controls (BMI $<30\text{kg/m}^2$) free of HF undergoing identical evaluation during the same period. Control subjects were required to

display no demonstrable cardiac pathology after thorough clinical evaluation, imaging and invasive assessment, including normal rest and exercise PCWP (criteria above). The Mayo Clinic Institutional Review Board approved the study and written informed consent was provided by all subjects. The authors had full access to the data and take responsibility for its integrity.

Clinical Assessment

Clinical history, laboratory data and current medications were abstracted from the medical records. Ideal body weight was calculated based on height ($a + b \times [\text{height in cm} - 150]$, where $a = 48$ for men and 45 for women, and $b = 1.1$ for men and 0.9 for women, respectively).⁷ Plasma volume was estimated by $(1 - \text{hematocrit}) \times (a + [b \times \text{weight in kg}])$ where $a = 1530$ for men and 864 for women, and $b = 41$ for men and 47.9 for women, respectively.⁸

Assessment of Cardiac Structure and Function

Two-dimensional, M-mode, Doppler and tissue Doppler echocardiography was performed within four weeks of catheterization according to the American Society of Echocardiography guidelines.⁹ Echocardiographic measurements were performed retrospectively by an experienced investigator (MO) in a blinded fashion. LV mass was indexed to height^{2,7,10} Myocardial deformation analyses were performed offline, using commercially available software (Syngo, Siemens Medical Solutions Munich, Germany). LV longitudinal strain was measured from two apical views as previously described.^{11, 12} Strain values represent the mean of three beats.

Right ventricular (RV) basal, mid-cavity, and longitudinal dimensions were measured at end-diastole using RV-focused views. Because adequate images for RV strain, tissue Doppler and m-mode echocardiography were unavailable, RV systolic function was assessed by RV fractional area change.¹³ Total epicardial volume was estimated from two hemi-ellipsoids containing both atria and ventricles using the apical 4-chamber view.¹⁴ Epicardial fat thickness was measured on the free wall of the RV at end-systole as previously described.¹⁵

Assessment of Ventricular Interaction and Pericardial Restraint

To quantify the degree of coupling between the left and right ventricles in the pericardial space (ventricular interaction), we measured simultaneous right and left heart filling pressures (below) and the configuration of the septum on echocardiography. As pericardial restraint and ventricular interaction increase, the pressure gradient between the LV and RV decreases, and the septum becomes less convex toward the RV, causing the LV to assume a 'D shape' in the short axis view.

To quantify the magnitude of ventricular interaction, septal wall configuration was measured using two methods as shown in Supplemental Figure 1.^{13, 16} The LV diameter bisecting and perpendicular to the interventricular septum (septolateral dimension, SL) was measured in the parasternal short axis view, along with the diameter 90° orthogonal to the SL in the anteroposterior dimension (AP). The eccentricity index was then calculated as AP/SL.

Eccentricity index values exceeding unity indicate greater septal flattening and enhanced ventricular interdependence.

As another assessment of septal configuration, the area of the LV in the short axis view was measured by planimetry (Supplemental Figure 1). An idealized radius was calculated from the planimetric area assuming the LV to be perfectly circular ($R_{ideal} = A/\pi$). Actual LV radius was defined as length from the center of LV cavity to the septum (R_{actual}). The center of the LV was defined by the perpendicular bisection of the SL and AP dimensions. The ratio of R_{ideal} to R_{actual} was calculated. Values of R_{ideal}/R_{actual} exceeding unity indicate greater septal shifting toward the LV cavity and enhanced interdependence (Supplemental Figure 1).

Catheterization Protocol

Patients were studied on their chronic medications in the fasted state after minimal sedation in the supine position as previously described.^{17–19} Right heart catheterization was performed through a 9 Fr sheath via the right internal jugular vein. Pressures in the right atrium (RA), pulmonary artery (PA), and pulmonary capillary wedge pressure (PCWP) were measured at end expiration (mean of 3 beats). LV transmural pressure (LVTMP), which reflects LV preload independent of right heart filling pressure and pericardial restraint, was estimated as PCWP - RA pressure.^{20, 21} Following baseline hemodynamic assessment, subjects underwent maximal-effort invasive exercise assessment. The first stage exercise at 20W exercise was performed for 5 min, and this was followed by 10–20W increments in workload (3 minute stages) to subject-reported exhaustion. Pressure tracings were digitized and stored for offline analysis by one investigator with experience in invasive hemodynamic assessment (BAB).

Oxygen consumption (VO_2) was measured from expired gas analysis (MedGraphics, St. Paul, MN). Arterial and mixed venous blood was directly sampled to measure oxygen content (saturation $\times$ hemoglobin $\times$ 1.34). Arterial-venous O_2 content difference (AVO_{2diff}) was calculated as the difference between systemic and PA O_2 contents. Cardiac output (CO) was determined by the Fick method ($CO = VO_2 / AVO_{2diff}$) and was scaled to body surface area to determine cardiac index (CI).

Pulmonary and systemic vascular function were assessed by pulmonary vascular resistance index ($PVRI = [\text{mean PA-PCWP}]/CI$), PA compliance index ($PACI = SVI/[\text{PA pulse pressure}]$), systemic vascular resistance index ($SVRI = [\text{mean arterial BP-RA}] \times 79.9/CI$), total arterial compliance index ($TACI = SVI/\text{systemic pulse pressure}$) and effective arterial elastance index ($EaI = [0.9 \times \text{systolic BP}]/SVI$).

The LV end-diastolic pressure (EDP), end-diastolic volume (EDV) relationship ($EDP = \alpha \cdot EDV^\beta$) was assessed using invasive PCWP and echocardiographic LV volumes according to the single beat method of Klotz et al.²² This analysis yields the LV stiffness constant β , which increases with elevations in LV chamber stiffness, and a predicted LVEDV at common PCWP of 30 mmHg (V_{30}) which decreases as diastolic LV chamber capacitance decreases.

Statistical Analysis

Data are reported as mean (SD), median (IQR) or number (%) unless otherwise specified. Between-group differences were compared by 1-way ANOVA, Kruskal-Wallis test, or chi-square test, as appropriate. The Tukey's HSD test or Steel-Dwass test was used to adjust for multiple testing. Linear and non-linear regressions were used to assess associations between two variables. Linear regression models with an interaction term were performed to test the difference in the relationship between dependent and independent variables between two groups. For non-normally distributed variables entered into regression models, the assumption of normally distributed residuals was verified by Quantile plots, and no violations were observed.

RESULTS

Subject Characteristics

Subjects with non-obese HFpEF were older, but sex, height, and ideal body weight were similar across groups (Table 1). Actual body weight, BMI, body surface area, and estimated plasma volume were greater in obese HFpEF compared to non-obese HFpEF and controls. As compared to controls, HFpEF subjects displayed higher prevalence of comorbidities and were more treated with HF medicines. Diabetes and sleep apnea were more prevalent in obesity-related HFpEF, whereas atrial fibrillation was more common in non-obese HFpEF. Hemoglobin and eGFR were lower and NT-proBNP was higher in the HFpEF groups compared with controls, but natriuretic peptide levels were lower in obese HFpEF compared to non-obese HFpEF (Table 1).

Cardiac Structure and Function

As compared to non-obese HFpEF and controls, subjects with obese HFpEF had larger LV dimensions, volumes and mass, with increased LV mass to volume ratio indicating greater concentric remodeling (Table 2). LV volumes scaled to BSA in obese HFpEF were not different from non-obese HFpEF or controls.

While LVEF was similar in the 3 groups, LV systolic function was impaired in both obese and non-obese HFpEF groups as compared to controls, evidenced by decreased longitudinal strain (Table 2). Doppler estimates of diastolic function and filling pressures were similarly abnormal in the HFpEF groups as compared to controls.

RV size was significantly larger in obese HFpEF compared to both controls and non-obese HFpEF (Table 2). This remained significant after adjusting for the prevalence of sleep apnea (not shown). RV systolic function assessed by FAC was depressed in obese HFpEF as compared to controls. RV size was directly correlated with body mass (Figure 1A) but not height (not shown).

Resting Hemodynamics and Oxygen Consumption

Compared to non-obese HFpEF and controls, subjects with obese HFpEF displayed higher RA pressures and PCWP at rest (Table 3). Pulmonary capillary wedge pressure was directly correlated with NT-proBNP in all HFpEF subjects, but the relationship was shifted upward

in obese HFpEF, meaning that PCWP was higher for any given NT-proBNP value in obese HFpEF subjects (Figure 1C). In contrast, the relationship between NT-proBNP and LVTMP, which more accurately reflects LV distending pressure after accounting for external pericardial constraint, was not different between in obese and non-obese HFpEF subjects (Figure 1D).

In obese HFpEF, elevations in PCWP were directly correlated with greater body mass and estimated plasma volume (Figure 2). However, PCWP bore no relationship to body size or plasma volume in non-obese HFpEF.

Pulmonary artery pressures were elevated at rest in obese and non-obese HFpEF subjects owing to high PCWP and higher PVRI (Table 3). In contrast, SVRI, EaI, and systemic and pulmonary arterial compliances were similar in the HFpEF and control groups at rest (Table 3). VO_2 indexed to body weight was lower in obese HFpEF compared to controls and non-obese HFpEF, suggesting a lower proportion of metabolically active tissue. Resting AVO_2 difference was similar in the 3 groups.

Exercise Capacity and Hemodynamics

Peak exercise workload achieved was lower in subjects with obese HFpEF and non-obese HFpEF as compared to controls (36 ± 17 and 39 ± 19 vs 69 ± 29 W, $p < 0.0001$). This was related to limited ability to augment cardiac output with exercise, which was similarly impaired in obese and non-obese HFpEF (Figure 3A). The efficiency of translating metabolic work (VO_2) to external ergometric work (cycling Watts) was lower in obese HFpEF as compared to both non-obese HFpEF and controls (Figure 3B). This led to a lower peak VO_2 in obese HFpEF as compared to both non-obese HFpEF and controls (Table 3). Peak VO_2 achieved during exercise testing was inversely correlated with body weight (Figure 3C). There were no group differences in exercise AVO_2 difference between HFpEF and control subjects (Table 3).

With exercise, left and right heart filling pressures were higher in obese HFpEF as compared to both non-obese HFpEF and controls (Table 3). Exercise-induced pulmonary hypertension was also most profound in the obese HFpEF group (Figure 3). This was related to greater increases in PCWP as well as impaired pulmonary vasodilation, manifest by greater decreases in PA compliance and less reduction in PVRI with exertion in obese HFpEF as compared to non-obese HFpEF and controls (Figure 3). Obese HFpEF subjects also displayed more chronotropic incompetence and higher exercise BP compared to controls (Table 3).

Myocardial, Pericardial and Ventricular Interactions

Left ventricular diastolic stiffness (β) was increased and V_{30} indexed to body size was reduced in both obese and non-obese HFpEF as compared to controls, in keeping with significant diastolic dysfunction in all HFpEF subjects (Table 3). Epicardial fat thickness was 20 and 50% higher in obese HFpEF as compared to non-obese HFpEF and controls, respectively (Table 2). The latter, in tandem with greater biventricular hypertrophy observed in obese HFpEF (Table 2), led to marked increases in total epicardial heart volume in obese

HFpEF that greatly exceeded values observed in both non-obese HFpEF and controls (Table 2, Figure 1 and 4).

Chronic increases in heart volume cause secondary pericardial dilation, but if this dilation is not matched to increases in heart size and epicardial fat thickness, there can be greater coupling between the pericardium, right heart and left heart (ventricular interaction). As compared to both non-obese HFpEF and controls, obese HFpEF subjects displayed significantly enhanced ventricular interaction and pericardial restraint. This was evidenced by the greater septal flattening with obesity-related HFpEF (less convex to the RV, quantified by higher LV eccentricity index and higher ideal/actual LV radius), by a higher ratio of RA to PCWP at rest and during exercise (Table 2, Figure 4).

LV eccentricity was greater in obese HFpEF for any given value of PA pressure, indicating that ventricular interdependence and septal distortion in obese HFpEF was not simply related to greater RV afterload from pulmonary hypertension (Figure 5). However, the increase in LV eccentricity (and thus interdependence) was amplified to greater extent in obese HFpEF subjects as RV afterload increases compared to non-obese subjects (interaction $p < 0.05$ for both, Figure 5).

Right atrial pressure (which approximates pericardial pressure) was greater in obese HFpEF relative to total body VO_2 at rest and during exercise (Figure 5). Right atrial pressure was also directly correlated with LV eccentricity index ($r = 0.36$, $p < 0.0001$) and total heart volume ($r = 0.34$, $p < 0.0001$). The PCWP required to achieve any given distending LV pressure (transmural pressure, LVTMP) was increased in obese HFpEF compared to non-obese HFpEF or controls (Figure 5).

DISCUSSION

In the current study, we assessed cardiovascular structure, function, exercise capacity and reserve in subjects with obesity-related HFpEF as compared to individuals with non-obese HFpEF and controls without HF. Subjects with obese HFpEF displayed greater plasma volume expansion, more biventricular remodeling, greater right ventricular dysfunction, worse exercise capacity, more profound hemodynamic derangements on exercise, and impaired pulmonary vasodilation. While LV diastolic function was impaired and filling pressures were elevated in HFpEF subjects regardless of adiposity, obese HFpEF subjects displayed additional contributors to high LV filling pressures, including greater dependence on plasma volume expansion, increased pericardial restraint, and enhanced ventricular interaction, which was synergistically amplified with increasing right ventricular afterload. These data provide compelling evidence that patients with the obese HFpEF phenotype have bona fide HF, and identifies distinct mechanisms that provide therapeutic targets for improving symptoms and outcomes in this common HFpEF phenotype.

Obesity and HFpEF

Obesity is a major risk factor for HF.²³ Unlike other cardiovascular diseases such as coronary disease and stroke, this excess risk is not explained by traditional risk factors.²⁴ Increases in body fat cause hemodynamic, metabolic, inflammatory and hormonal

perturbations that stress the heart and vasculature.^{5, 25} Recent studies have clearly shown that obesity and weight gain promote abnormalities in myocardial structure and function implicated in the development of HFpEF.²⁶⁻³²

Obesity is highly prevalent in the western world, and this prevalence is even greater in patients with HFpEF.^{25, 33} Over 80% of patients with HFpEF are either overweight or obese,² and in a recently-reported trial the average BMI in the HFpEF subjects exceeded 35 kg/m².³⁴ Opinions about the importance of obesity in HFpEF have shifted in recent years. Earlier studies suggested that symptoms of dyspnea in obese patients were likely simply related to excess body mass and not cardiac abnormalities,³⁵ but current disease paradigms have begun to embrace the importance of obesity in the pathophysiology of HFpEF, particularly as a cause of systemic inflammation, oxidative stress, and depressed nitric oxide availability that drives cardiac and extracardiac manifestations of disease.² A recent series has demonstrated that higher body mass is one of the strongest independent correlates of symptom severity in people with HFpEF,³⁶ but no study has reported a detailed pathophysiologic characterization of the impact of severe obesity amongst patients with HFpEF.

Pathophysiologic Features of Obesity-Related HFpEF

The increases in blood volume and thus cardiac loading in obesity may cause structural and functional alterations that contribute to HF.^{4, 6, 8} Previous studies have reported that subjects with HFpEF may display increased LV diastolic diameter and plasma volume compared to controls.^{37, 38} In accordance with this, we demonstrated that subjects with obese HFpEF had greater estimated plasma volume, LV remodeling, RV enlargement, and increased total heart volume as compared to non-obese HFpEF. The LV in obese HFpEF displayed dilation but also an increase in the ratio of LV mass to volume, indicating concentric remodeling was present.

Elevation in filling pressures was positively correlated with increased body mass and plasma volume in obese HFpEF, but not in non-obese HFpEF (interaction $p=0.007$, Figure 2). This indicates that the volume overload present in obesity contributes to chamber remodeling and hemodynamic derangements observed in obesity-related HFpEF. These data emphasize that obese HFpEF patients have unequivocal, objective evidence of cardiac failure that is linked to adiposity and contributes to symptoms. In other words, obese HFpEF patients are not simply limited by the mechanical effects of increased body mass, but increased body mass drives hemodynamic severity of HF by its effects on the cardiovascular system.

Left ventricular diastolic dysfunction is a fundamental mechanism of HFpEF, and we confirm previous studies by showing that diastolic function was impaired in both obese and non-obese subjects as compared to controls, evidenced by increased chamber stiffness (β) and lower chamber volume at a common PCWP (V_{30} index).³⁹ In addition to LV diastolic dysfunction, we show for the first time that enhanced ventricular interaction also plays an important role in obesity-related HFpEF. The increases in chamber volumes, wall thickness and epicardial fat observed in obese HFpEF subjects caused a significant increase in total heart volume, consistent with a previous report.¹⁴ Chronic increases in heart volume and

epicardial fat may increase pericardial restraint and enhance ventricular interaction if the pericardium does not dilate as much as the heart grows. We observed these findings to be present in the obese HFpEF subjects.

The true distending pressure that drives LV filling, or LV transmural pressure, is defined as intracavitary pressure (LVEDP or PCWP) minus the external pressure applied to the LV from the pericardium and right heart.⁴⁰ Previous studies have demonstrated that pericardial pressure is best approximated by RA pressure,²⁰ which was elevated to greater extent at rest and during exercise in obese HFpEF compared to non-obese HFpEF and controls. This alone suggests greater pericardial restraint in obese HFpEF.

The degree of pericardial restraint and ventricular interaction was further assessed in our study by examining the ratio of RA pressure to PCWP at rest and during exercise, and by measuring the shape and configuration of the interventricular septum. In the unloaded heart, the septum occupies a neutral position between the LV and RV, but because LV pressure normally exceeds RV pressure during diastole, the septum is normally convex to the RV.⁴¹ As ventricular interaction increases, the RV and LV compete for limited space in the pericardium. Pressures equilibrate in both sides of the heart because the pericardium limits further cardiac expansion when restraint is increased.⁴⁰ The RA/PCWP ratio approaches unity and the septum becomes flattened and less convex to the RV.^{16, 42} Each of these changes was observed in the obese HFpEF subjects as compared to both non-obese HFpEF and controls in the current study, with higher RA/PCWP ratio and increase in LV eccentricity due to a change in septal configuration.

Notably, exercise PCWP was higher in obese HFpEF than in non-obese HFpEF despite similar LV transmural pressure. This suggests uncoupling between LV filling pressure (PCWP) and LV preload (end diastolic volume) in addition to abnormalities related to passive LV stiffening.⁴⁰ This is similar to hemodynamic abnormalities seen in other conditions characterized by enhanced ventricular interdependence, including right-sided heart failure from tricuspid insufficiency²¹ or advanced HFrEF.⁴³ The higher PCWP required to achieve a given distending LV transmural pressure (Figure 5) leads to greater hydrostatic pressure in the pulmonary capillaries in obese HFpEF patients that promotes dyspnea, and steeper increase in PA pressures, which may contribute to greater abnormalities in RV-PA coupling in obese HFpEF.

Reserve Limitations in Obese HFpEF

We observed significant limitations in cardiac reserve and aerobic capacity in obese HFpEF, with higher filling pressures and more severe pulmonary vascular disease. These limitations in ventricular reserve in obese HFpEF may be related in part to reductions in cardiac efficiency. In obese women without HF, myocardial oxygen consumption is increased, and this is associated with reduced cardiac efficiency and increase reliance on fatty acid oxidation for energy.⁴⁴ These changes in myocardial substrate utilization may also be seen in patients with increased epicardial fat, as noted in the current study.⁴⁵ Impairments in myocardial oxygen utilization during exercise have also been described in patients with HFpEF, and this may be more profound in obesity-related HFpEF.⁴⁶ We also observed that

the efficiency of converting metabolic energy (VO_2) to mechanical locomotion (Watts performed) was reduced in HFpEF, further contributing to functional limitation.

Prior studies have shown that RV function is impaired in HFpEF,⁴⁷ and we observed that RV dysfunction was even more pronounced in obese HFpEF subjects. Part of the RV dysfunction may be related to remodeling from increased body mass (Figure 1), but it seems likely that greater RV afterload may also contribute, particularly given the heightened afterload sensitivity of the RV in HFpEF.⁴⁷ While PA pressures were similar at rest in obese and non-obese HFpEF, there was greater exercise-induced elevation in PA pressures in obese HFpEF patients, related to higher PCWP as well as inadequate pulmonary vasodilation (Figure 3). The causes for this inadequate vasodilation are unclear, but could relate to vasoactive adipokines that reduce nitric oxide bioavailability^{48, 49} or pulmonary endothelial dysfunction secondary to metabolic syndrome.⁵⁰ Space limitations in the cardiac fossa from cardiomegaly and increased epicardial fat may become even more problematic during exercise as RV size increases due to heightened venous return and worsening pulmonary hypertension. This may explain the greater RA (and thus pericardial) pressure and increased ratio of RA to PCWP on exercise in subjects with obese HFpEF. Indeed, the increase in ventricular interaction was amplified more dramatically in obese HFpEF subjects as PA pressures rose as compared to non-obese HFpEF (Figure 5). This identifies a pathologic synergy between pericardial restraint, volume overload and abnormal RV-PA coupling that may be more problematic in patients with obesity-related HFpEF.

Clinical Implications

Beyond the aforementioned pathophysiologic observations, these data have a number of potentially important clinical implications. Plasma NT-proBNP levels were correlated with filling pressures in all HFpEF subjects, but the relationship was shifted upward in obese subjects such that for any NT-proBNP level, PCWP were higher in the presence of obesity (Figure 1C). It is well known that natriuretic peptide levels are lower in obese as compared to non-obese patients.⁵¹ This has previously been attributed to enhanced natriuretic peptide degradation in fat tissue, alterations in sex hormones,^{52, 53} or insulin resistance.⁵⁴

Diastolic wall stress is the primary stimulus for B-type natriuretic peptide release, and wall stress is reduced as external pressure applied to the ventricle increases. In contrast to the differential relationship between PCWP and NT-proBNP, in obese and non-obese HFpEF, correlations between LV distending pressure (LVTMP) and NT-proBNP were virtually superimposable in these groups (Figure 1D). Collectively these data provide an alternative mechanism by which NT-proBNP levels are lowered in obesity: since increased epicardial fat and heightened pericardial restraint were observed in this cohort, this may reduce wall stress and thus ventricular elaboration of natriuretic peptides. An important ramification of this finding is that PCWP, which is the gold standard lynchpin measure for HFpEF, is much higher for any NT-proBNP level in the presence of obesity. These data have important implications for routine clinical care, as well as design and entry criteria for clinical trials in HFpEF. They also suggest that patients with obesity and increased pericardial restraint might suffer from some degree of natriuretic peptide deficiency, which could potentially explain some of the greater plasma volume excess noted.

Recent data indicate that in addition to the amount of fat, the location of adipose tissue may be very important in obesity-related disorders, whether it involves the liver, kidney or skeletal muscle, and each of these may also be important in the pathophysiology of obese HFpEF.^{25, 55} Similarly, it is known that epicardial fat acts as a metabolically active depot that affects the myocardium via production of inflammatory cytokines.⁴⁵ Because obese HFpEF subjects displayed more epicardial adipose, it is likely that they were more exposed to cytokines released from this depot that could have adverse effects on cardiac function. In addition to these endocrine effects, the current data are the first to identify a deleterious mechanical effect of epicardial fat, as it functions like a “space occupying lesion” in the cardiac fossa that may contribute to the increase intracardiac pressures in obese HFpEF, particularly during exercise. Further study is warranted to determine whether interventions to reduce or even resect epicardial fat might be beneficial in patients with obese HFpEF, where this tissue may occupy a substantial proportion of pericardial volume.

Overall, the myriad of pathophysiologic differences observed between obese and non-obese HFpEF support the notion that the two entities should be considered to some extent as sub-phenotypes, though clearly many interventions will be effective for all patients regardless of the presence or absence of obesity. This may be important to design optimal treatments, as one of the reasons suggested to explain the failure of prior trials in HFpEF has been related to pathophysiologic heterogeneity in this clinical syndrome. For example, the hypervolemic state, cardiomegaly, pericardial restraint, and stronger relationships between filling pressures and estimated plasma volume all suggest that obese HFpEF patients may be better poised to respond to diuretics or other volume reducing therapies, such as SGLT-2 inhibitors. The abnormalities in RV-PA coupling observed in obese HFpEF suggest potential for greater benefit from pulmonary vasodilators. Finally, in addition to targeting epicardial fat as described above, therapies aimed at reducing overall body mass might be effective. In this regard, Kitzman and colleagues recently demonstrated that weight loss induced by caloric restriction reduced LV mass and inflammatory markers, improved exercise capacity, and enhanced quality of life in patients with obese HFpEF (mean BMI 38).⁵⁶ Similarly, bariatric surgery has been observed to improve functional capacity in patients with HFrEF. Prospective trials testing weight loss using other behavioral, pharmacologic or surgical interventions are clearly warranted in patients with obesity-related HFpEF.

Limitations

This is a single center study from a tertiary referral center and as such has inherent flaws related to selection and referral bias. In obesity, the problem of scaling heart size or mass for body size is complex. Body surface area is often chosen as the index of body size. However, it might underestimate changes in heart because body surface area increases more than those in heart.¹⁰ RV function was assessed using fractional area change only because adequate images for strain imaging or tricuspid annular excursion were not available. The control group was not truly normal in that they had prevalent comorbidities such as hypertension, had somewhat reduced longitudinal strain, and had been referred to invasive exercise stress testing, however this limitation would only be expected to bias our results toward the null.

Conclusions

Patients with obesity-related HFpEF display unique pathophysiologic features including greater biventricular remodeling, volume overload, more right ventricular dysfunction, greater ventricular interaction and pericardial restraint, worse exercise capacity, more profound hemodynamic derangements, and impaired pulmonary vasodilation. These distinctions suggest that obesity may be considered as a specific HFpEF phenotype. Further study is required to delineate the cellular pathophysiology of obese HFpEF and to define the role for novel therapies targeting weight loss and other sequelae of obesity in HFpEF.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Source of funding

Dr. Borlaug is supported by U10 HL110262 and RO1 HL128526, and Dr. Reddy is supported by T32 HL007111.

References

1. Reddy YN, Borlaug BA. Heart failure with preserved ejection fraction. *Curr Probl Cardiol*. 2016; 41:145–188. [PubMed: 26952248]
2. Shah SJ, Kitzman DW, Borlaug BA, van Heerebeek L, Zile MR, Kass DA, Paulus WJ. Phenotype-specific treatment of heart failure with preserved ejection fraction: A multiorgan roadmap. *Circulation*. 2016; 134:73–90. [PubMed: 27358439]
3. Go AS, Mozaffarian D, Roger VL, Benjamin EJ, Berry JD, Blaha MJ, Dai S, Ford ES, Fox CS, Franco S, Fullerton HJ, Gillespie C, Hailpern SM, Heit JA, Howard VJ, Huffman MD, Judd SE, Kissela BM, Kittner SJ, Lackland DT, Lichtman JH, Lisabeth LD, Mackey RH, Magid DJ, Marcus GM, Marelli A, Matchar DB, McGuire DK, Mohler ER 3rd, Moy CS, Mussolino ME, Neumar RW, Nichol G, Pandey DK, Paynter NP, Reeves MJ, Sorlie PD, Stein J, Towfighi A, Turan TN, Virani SS, Wong ND, Woo D, Turner MB. Heart disease and stroke statistics--2014 update: A report from the american heart association. *Circulation*. 2014; 129:e28–e292. [PubMed: 24352519]
4. Lauer MS, Anderson KM, Kannel WB, Levy D. The impact of obesity on left ventricular mass, geometry The framingham heart study. *JAMA*. 1991; 266:231–236. [PubMed: 1829117]
5. Abel ED, Litwin SE, Sweeney G. Cardiac remodeling in obesity. *Physiol Rev*. 2008; 88:389–419. [PubMed: 18391168]
6. Lavie CJ, Alpert MA, Arena R, Mehra MR, Milani RV, Ventura HO. Impact of obesity and the obesity paradox on prevalence and prognosis in heart failure. *JACC Heart Fail*. 2013; 1:93–102. [PubMed: 24621833]
7. Hammond, KA. Dietary and clinical assessment. In: Mahan, LK., Stump, SE., editors. *Krause's food, nutrition, & diet therapy*. Philadelphia: Saunders; 2000. p. 353-379.
8. Reddy YN, Melenovsky V, Redfield MM, Nishimura RA, Borlaug BA. High-output heart failure: A 15-year experience. *J Am Coll Cardiol*. 2016; 68:473–482. [PubMed: 27470455]
9. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, Flachskampf FA, Foster E, Goldstein SA, Kuznetsova T, Lancellotti P, Muraru D, Picard MH, Rietzschel ER, Rudski L, Spencer KT, Tsang W, Voigt JU. Recommendations for cardiac chamber quantification by echocardiography in adults: An update from the american society of echocardiography and the european association of cardiovascular imaging. *Eur Heart J Cardiovasc Imaging*. 2015; 16:233–270. [PubMed: 25712077]

10. de Simone G, Devereux RB, Roman MJ, Alderman MH, Laragh JH. Relation of obesity and gender to left ventricular hypertrophy in normotensive and hypertensive adults. *Hypertension*. 1994; 23:600–606. [PubMed: 8175168]
11. Shah AM, Claggett B, Sweitzer NK, Shah SJ, Anand IS, Liu L, Pitt B, Pfeffer MA, Solomon SD. Prognostic importance of impaired systolic function in heart failure with preserved ejection fraction and the impact of spironolactone. *Circulation*. 2015; 132:402–414. [PubMed: 26130119]
12. Fine NM, Shah AA, Han IY, Yu Y, Hsiao JF, Koshino Y, Saleh HK, Miller FA Jr, Oh JK, Pellikka PA, Villarraga HR. Left and right ventricular strain and strain rate measurement in normal adults using velocity vector imaging: An assessment of reference values and intersystem agreement. *Int J Cardiovasc Imaging*. 2013; 29:571–580. [PubMed: 22976877]
13. Rudski LG, Lai WW, Afilalo J, Hua L, Handschumacher MD, Chandrasekaran K, Solomon SD, Louie EK, Schiller NB. Guidelines for the echocardiographic assessment of the right heart in adults: A report from the american society of echocardiography endorsed by the european association of echocardiography, a registered branch of the european society of cardiology, and the canadian society of echocardiography. *J Am Soc Echocardiogr*. 2010; 23:685–713. quiz 786–688. [PubMed: 20620859]
14. Melenovsky V, Borlaug BA, Rosen B, Hay I, Ferruci L, Morell CH, Lakatta EG, Najjar SS, Kass DA. Cardiovascular features of heart failure with preserved ejection fraction versus nonfailing hypertensive left ventricular hypertrophy in the urban baltimore community: The role of atrial remodeling/dysfunction. *J Am Coll Cardiol*. 2007; 49:198–207. [PubMed: 17222731]
15. Iacobellis G. Relation of epicardial fat thickness to right ventricular cavity size in obese subjects. *Am J Cardiol*. 2009; 104:1601–1602. [PubMed: 19932799]
16. Ryan T, Petrovic O, Dillon JC, Feigenbaum H, Conley MJ, Armstrong WF. An echocardiographic index for separation of right ventricular volume and pressure overload. *Journal of the American College of Cardiology*. 1985; 5:918–927. [PubMed: 3973294]
17. Borlaug BA, Melenovsky V, Koepp KE. Inhaled sodium nitrite improves rest and exercise hemodynamics in heart failure with preserved ejection fraction. *Circ Res*. 2016; 119:880–886. [PubMed: 27458234]
18. Borlaug BA, Kane GC, Melenovsky V, Olson TP. Abnormal right ventricular-pulmonary artery coupling with exercise in heart failure with preserved ejection fraction. *Eur Heart J*. 2016; 37:3293–3302.
19. Borlaug BA, Koepp KE, Melenovsky V. Sodium nitrite improves exercise hemodynamics and ventricular performance in heart failure with preserved ejection fraction. *J Am Coll Cardiol*. 2015; 66:1672–1682. [PubMed: 26449137]
20. Tyberg JV, Taichman GC, Smith ER, Douglas NW, Smiseth OA, Keon WJ. The relationship between pericardial pressure and right atrial pressure: An intraoperative study. *Circulation*. 1986; 73:428–432. [PubMed: 3948353]
21. Andersen MJ, Nishimura RA, Borlaug BA. The hemodynamic basis of exercise intolerance in tricuspid regurgitation. *Circ Heart Fail*. 2014; 7:911–917. [PubMed: 25190672]
22. Klotz S, Hay I, Zhang G, Maurer M, Wang J, Burkoff D. Development of heart failure in chronic hypertensive dahl rats: Focus on heart failure with preserved ejection fraction. *Hypertension*. 2006; 47:901–911. [PubMed: 16585423]
23. Kenchaiah S, Evans JC, Levy D, Wilson PW, Benjamin EJ, Larson MG, Kannel WB, Vasan RS. Obesity and the risk of heart failure. *N Engl J Med*. 2002; 347:305–313. [PubMed: 12151467]
24. Ndumele CE, Matsushita K, Lazo M, Bello N, Blumenthal RS, Gerstenblith G, Nambi V, Ballantyne CM, Solomon SD, Selvin E, Folsom AR, Coresh J. Obesity and subtypes of incident cardiovascular disease. *J Am Heart Assoc*. 2016; 5:e003921. [PubMed: 27468925]
25. Kitzman DW, Shah SJ. The hfpef obesity phenotype: The elephant in the room. *J Am Coll Cardiol*. 2016; 68:200–203. [PubMed: 27386774]
26. Wong CY, O'Moore-Sullivan T, Leano R, Byrne N, Beller E, Marwick TH. Alterations of left ventricular myocardial characteristics associated with obesity. *Circulation*. 2004; 110:3081–3087. [PubMed: 15520317]

27. Russo C, Jin Z, Homma S, Rundek T, Elkind MS, Sacco RL, Di Tullio MR. Effect of obesity and overweight on left ventricular diastolic function: A community-based study in an elderly cohort. *J Am Coll Cardiol*. 2011; 57:1368–1374. [PubMed: 21414533]
28. Borlaug BA, Redfield MM, Melenovsky V, Kane GC, Karon BL, Jacobsen SJ, Rodeheffer RJ. Longitudinal changes in left ventricular stiffness: A community-based study. *Circ Heart Fail*. 2013; 6:944–952. [PubMed: 23811963]
29. Wohlfahrt P, Redfield MM, Lopez-Jimenez F, Melenovsky V, Kane GC, Rodeheffer RJ, Borlaug BA. Impact of general and central adiposity on ventricular-arterial aging in women and men. *JACC Heart Failure*. 2014; 2:489–499. [PubMed: 25194285]
30. Bello NA, Cheng S, Claggett B, Shah AM, Ndumele CE, Roca GQ, Santos AB, Gupta D, Vardeny O, Aguilar D, Folsom AR, Butler KR, Kitzman DW, Coresh J, Solomon SD. Association of weight and body composition on cardiac structure and function in the aric study (atherosclerosis risk in communities). *Circ Heart Fail*. 2016; 9:e002978. [PubMed: 27512104]
31. Selvaraj S, Martinez EE, Aguilar FG, Kim KY, Peng J, Sha J, Irvin MR, Lewis CE, Hunt SC, Arnett DK, Shah SJ. Association of central adiposity with adverse cardiac mechanics: Findings from the hypertension genetic epidemiology network study. *Circ Cardiovasc Imaging*. 2016; 9:e004396. [PubMed: 27307550]
32. Russo C, Sera F, Jin Z, Palmieri V, Homma S, Rundek T, Elkind MS, Sacco RL, Di Tullio MR. Abdominal adiposity, general obesity, and subclinical systolic dysfunction in the elderly: A population-based cohort study. *Eur J Heart Fail*. 2016; 18:537–544. [PubMed: 27109744]
33. Flegal KM, Carroll MD, Kit BK, Ogden CL. Prevalence of obesity and trends in the distribution of body mass index among us adults, 1999–2010. *JAMA*. 2012; 307:491–497. [PubMed: 22253363]
34. Redfield MM, Anstrom KJ, Levine JA, Koepf GA, Borlaug BA, Chen HH, LeWinter MM, Joseph SM, Shah SJ, Semigran MJ, Felker GM, Cole RT, Reeves GR, Tedford RJ, Tang WH, McNulty SE, Velazquez EJ, Shah MR, Braunwald E. Isosorbide mononitrate in heart failure with preserved ejection fraction. *N Engl J Med*. 2015; 373:2314–2324. [PubMed: 26549714]
35. Caruana L, Petrie MC, Davie AP, McMurray JJ. Do patients with suspected heart failure and preserved left ventricular systolic function suffer from “diastolic heart failure” or from misdiagnosis? A prospective descriptive study. *BMJ*. 2000; 321:215–218. [PubMed: 10903655]
36. Dalos D, Mascherbauer J, Zotter-Tufaro C, Duca F, Kammerlander AA, Aschauer S, Bonderman D. Functional status, pulmonary artery pressure, and clinical outcomes in heart failure with preserved ejection fraction. *J Am Coll Cardiol*. 2016; 68:189–199. [PubMed: 27386773]
37. Maurer MS, King DL, El-Khoury Rumbarger L, Packer M, Burkhoff D. Left heart failure with a normal ejection fraction: Identification of different pathophysiologic mechanisms. *Journal of cardiac failure*. 2005; 11:177–187. [PubMed: 15812744]
38. Maurer MS, Burkhoff D, Fried LP, Gottdiener J, King DL, Kitzman DW. Ventricular structure and function in hypertensive participants with heart failure and a normal ejection fraction: The cardiovascular health study. *J Am Coll Cardiol*. 2007; 49:972–981. [PubMed: 17336721]
39. Lam CS, Roger VL, Rodeheffer RJ, Bursi F, Borlaug BA, Ommen SR, Kass DA, Redfield MM. Cardiac structure and ventricular-vascular function in persons with heart failure and preserved ejection fraction from olmsted county, minnesota. *Circulation*. 2007; 115:1982–1990. [PubMed: 17404159]
40. Tyberg, JV. Mechanical modulation of cardiac function: Role of the pericardium. In: Kohl, PSF., Franz, MR., editors. *New oxford textbook of cardiac mechano-electric feedback and arrhythmias*. Oxford, NY: Oxford University Press; 2011. p. 281-289.
41. Lima JA, Guzman PA, Yin FC, Brawley RK, Humphrey L, Traill TA, Lima SD, Marino P, Weisfeldt ML, Weiss JL. Septal geometry in the unloaded living human heart. *Circulation*. 1986; 74:463–468. [PubMed: 3742749]
42. Kingma I, Tyberg JV, Smith ER. Effects of diastolic transseptal pressure gradient on ventricular septal position and motion. *Circulation*. 1983; 68:1304–1314. [PubMed: 6640880]
43. Janicki JS. Influence of the pericardium and ventricular interdependence on left ventricular diastolic and systolic function in patients with heart failure. *Circulation*. 1990; 81:III15–20. [PubMed: 2297880]

44. Peterson LR, Herrero P, Schechtman KB, Racette SB, Waggoner AD, Kisrieva-Ware Z, Dence C, Klein S, Marsala J, Meyer T, Gropler RJ. Effect of obesity and insulin resistance on myocardial substrate metabolism and efficiency in young women. *Circulation*. 2004; 109:2191–2196. [PubMed: 15123530]
45. Iacobellis G, Corradi D, Sharma AM. Epicardial adipose tissue: Anatomic, biomolecular and clinical relationships with the heart. *Nat Clin Pract Cardiovasc Med*. 2005; 2:536–543. [PubMed: 16186852]
46. van Empel VP, Mariani J, Borlaug BA, Kaye DM. Impaired myocardial oxygen availability contributes to abnormal exercise hemodynamics in heart failure with preserved ejection fraction. *J Am Heart Assoc*. 2014; 3:e001293. [PubMed: 25468660]
47. Melenovsky V, Hwang SJ, Lin G, Redfield MM, Borlaug BA. Right heart dysfunction in heart failure with preserved ejection fraction. *Eur Heart J*. 2014; 35:3452–3462. [PubMed: 24875795]
48. Yudkin JS, Eringa E, Stehouwer CD. “Vasocrine” signalling from perivascular fat: A mechanism linking insulin resistance to vascular disease. *Lancet*. 2005; 365:1817–1820. [PubMed: 15910955]
49. Greenstein AS, Khavandi K, Withers SB, Sonoyama K, Clancy O, Jeziorska M, Laing I, Yates AP, Pemberton PW, Malik RA, Heagerty AM. Local inflammation and hypoxia abolish the protective anticontractile properties of perivascular fat in obese patients. *Circ Heart Fail*. 2009; 119:1661–1670.
50. Lai YC, Tabima DM, Dube JJ, Hughan KS, Vanderpool RR, Goncharov DA, St Croix CM, Garcia-Ocana A, Goncharova EA, Tofovic SP, Mora AL, Gladwin MT. Sirt3-amp-activated protein kinase activation by nitrite and metformin improves hyperglycemia and normalizes pulmonary hypertension associated with heart failure with preserved ejection fraction. *Circulation*. 2016; 133:717–731. [PubMed: 26813102]
51. Anjan VY, Loftus TM, Burke MA, Akhter N, Fonarow GC, Gheorghiade M, Shah SJ. Prevalence, clinical phenotype, and outcomes associated with normal b-type natriuretic peptide levels in heart failure with preserved ejection fraction. *Am J Cardiol*. 2012; 110:870–876. [PubMed: 22681864]
52. Lam CS, Cheng S, Choong K, Larson MG, Murabito JM, Newton-Cheh C, Bhasin S, McCabe EL, Miller KK, Redfield MM, Vasan RS, Coviello AD, Wang TJ. Influence of sex and hormone status on circulating natriuretic peptides. *J Am Coll Cardiol*. 2011; 58:618–626. [PubMed: 21798425]
53. Chang AY, Abdullah SM, Jain T, Stanek HG, Das SR, McGuire DK, Auchus RJ, de Lemos JA. Associations among androgens, estrogens, and natriuretic peptides in young women: Observations from the dallas heart study. *J Am Coll Cardiol*. 2007; 49:109–116. [PubMed: 17207730]
54. Khan AM, Cheng S, Magnusson M, Larson MG, Newton-Cheh C, McCabe EL, Coviello AD, Florez JC, Fox CS, Levy D, Robins SJ, Arora P, Bhasin S, Lam CS, Vasan RS, Melander O, Wang TJ. Cardiac natriuretic peptides, obesity, and insulin resistance: Evidence from two community-based studies. *J Clin Endocrinol Metab*. 2011; 96:3242–3249. [PubMed: 21849523]
55. Haykowsky MJ, Kouba EJ, Brubaker PH, Nicklas BJ, Eggebeen J, Kitzman DW. Skeletal muscle composition and its relation to exercise intolerance in older patients with heart failure and preserved ejection fraction. *Am J Cardiol*. 2014; 113:1211–1216. [PubMed: 24507172]
56. Kitzman DW, Brubaker P, Morgan T, Haykowsky M, Hundley G, Kraus WE, Eggebeen J, Nicklas BJ. Effect of caloric restriction or aerobic exercise training on peak oxygen consumption and quality of life in obese older patients with heart failure with preserved ejection fraction: A randomized clinical trial. *JAMA*. 2016; 315:36–46. [PubMed: 26746456]

Clinical Perspective

What is New?

- Obesity is common in heart failure with preserved ejection fraction (HFpEF) and has many cardiovascular effects, suggesting it may be a clinically relevant phenotype of HFpEF.
- Compared to non-obese HFpEF, obese HFpEF subjects display greater volume overload, more biventricular remodeling, greater right ventricular dysfunction, worse exercise capacity, more profound hemodynamic derangements, and impaired pulmonary vasodilation.
- Obese HFpEF subjects display other important contributors to high left filling pressures, including greater dependence on plasma volume expansion, increased pericardial restraint, and enhanced ventricular interaction, which is exaggerated as pulmonary pressure load increases.

What are the clinical implications?

- These data provide compelling evidence that patients with the obese HFpEF phenotype have bona fide HF, and display several pathophysiologic mechanisms that differ from non-obese patients with HFpEF.
- These data suggest a role for novel treatments targeting the unique features of obesity-related HFpEF in future trials.

Figure 1. Body mass, cardiac remodeling and relationships between NT-proBNP and LV filling pressures

(A, B) Increased body mass was associated with larger RV size and total heart volume. (C) Pulmonary capillary wedge pressure (PCWP) was directly correlated with NT-proBNP in all HFpEF subjects, but the relationship was shifted upward in obese HFpEF, indicating a higher PCWP for any value of NT-proBNP as compared to non-obese HFpEF. (D) In contrast, the correlations between left ventricular transmural pressure (LVTMP) and NT-proBNP did not differ in obese and non-obese HFpEF. HFpEF indicates heart failure with preserved ejection fraction; RV, right ventricular.

Figure 2. Correlations between left ventricular filling pressures, adiposity and plasma volume
Elevations in left heart filling pressures were related to greater body mass (**A**) and plasma volume (**B**) in obese HFpEF, but not in non-obese HFpEF. Abbreviations as in Figure 1.

Figure 3. Exercise capacity and hemodynamic reserve is reduced in obese HFpEF

(A) Compared to controls, increase in cardiac index was lower in both non-obese and obese HFpEF but similar between the groups. (B) The efficiency of translating metabolic work (VO_2) to external ergometric work (cycling Watts) was lower in obese HFpEF as compared to both non-obese HFpEF and controls. (C) Peak VO_2 was inversely correlated with body mass. (D) Peak exercise pulmonary artery mean pressure (mPAP) was higher in obese HFpEF than in both non-obese HFpEF and controls. This was explained by impaired pulmonary vasodilation with exercise in obese HFpEF as compared to both non-obese HFpEF and controls, evidenced by greater decreases in PA compliance index (PACI) and less reduction in pulmonary vascular resistance index (PVRI) (E–F). Error bars indicate SEM. * $p < 0.05$ vs. controls, † $p < 0.05$ vs. non-obese HFpEF. Abbreviations as in Figure 1.

Figure 4. Pericardial restraint and ventricular interdependence are enhanced in obese HFpEF
(A) Compared to non-obese HFpEF and control subjects, obese HFpEF displayed greater total epicardial heart volume. **(B)** Representative short-axis echocardiographic images of the mitral valve and mid cavity levels at end-diastole in obese HFpEF. The septum becomes flattened and less convex to the RV at end-diastole, indicative of enhanced ventricular interaction. **(C–D)** This was further supported by higher LV eccentricity index and right atrial pressure (RAP)/PCWP ratio in obese HFpEF as compared to non-obese HFpEF and control subjects. * $p < 0.05$ vs. controls; and † $p < 0.05$ vs. non-obese HFpEF. LV indicates left ventricular; and other abbreviation as in Figure 1.

Figure 5. Interactions between pericardial restraint, pulmonary artery pressures and filling pressures in obese HFpEF

(A–B) Compared to non-obese HFpEF, LV eccentricity index was greater in obese HFpEF for any given value of PA systolic pressure both at end-diastole and systole, suggesting that septal distortion in obese HFpEF was not simply related to more RV afterload mismatch. (C) The increase in RAP (which approximates pericardial pressure) relative to oxygen consumption (VO_2) was greater in obese HFpEF than in both non-obese HFpEF and control subjects with exercise. (D) The PCWP required to achieve any given distending LV pressure (transmural pressure, LVTMP) was shifted upward in obese HFpEF. See text for details.

* $p < 0.05$ vs. controls; and † $p < 0.05$ vs. non-obese HFpEF. Abbreviations as in Figures 1, 3, and 4.

Table 1**Baseline Characteristics**

	Controls (n=71)	Non-obese HFpEF (n=96)	Obese HFpEF (n=99)	P value
Age (years)	62±10	70±10 *	65±11 †	<0.0001
Female, n (%)	41 (58)	61 (64)	63 (64)	0.7
<i>Anthropometrics</i>				
Height (m)	1.7±0.1	1.7±0.1	1.7±0.1	0.3
Ideal body weight (kg)	66±14	64±12	64±13	0.4
Actual body weight (kg)	73±13	73±12	115±21 *†	<0.0001
Body mass index (kg/m ²)	25.4±2.8	26.0±2.7	40.8±5.6 *†	<0.0001
Body surface area (m ²)	1.8±0.2	1.8±0.2	2.2±0.2 *†	<0.0001
Estimated plasma volume (ml)	2680 (2380,3006)	2772 (2555,3133)	3907 (3563,4333) *†	<0.0001
<i>Comorbidities</i>				
Diabetes mellitus, n (%)	9 (13)	14 (15)	33 (33) *†	0.001
Hypertension, n (%)	51 (72)	77 (80)	81 (82)	0.3
Current atrial fibrillation, n (%)	3 (4)	18 (19) *	8 (8) †	0.006
Obstructive sleep apnea, n (%)	8 (11)	22 (23) *	58 (59) *†	<0.0001
<i>Medications</i>				
ACEI or ARB, n (%)	15 (21)	35 (37) *	49 (49) *†	0.001
Beta-blocker, n (%)	16 (23)	55 (58) *	51 (52) *†	<0.0001
Calcium channel blocker, n (%)	10 (14)	15 (16)	15 (15)	1.0
Loop Diuretic, n (%)	10 (14)	47 (49) *	52 (53) *†	<0.0001
<i>Laboratories</i>				
Hemoglobin (gm/dl)	12.9±1.3	12.1±1.3 *	12.2±1.5 *	0.0005
eGFR (ml/min/1.73m ²)	70±15	60±18 *	58±19 *	<0.0001
NT-proBNP (pg/ml)	89 (54,241)	633 (249,1545) *	213 (62,838) *†	<0.0001

Data are mean ± SD, median (interquartile range), or n (%). Final column reflects overall group differences.

* p<0.05 vs controls

† p<0.05 vs non-obese HFpEF.

ACEI indicates angiotensin-converting enzyme inhibitors; ARB, angiotensin-receptor blockers; eGFR, estimated glomerular filtration rate; HFpEF, heart failure with preserved ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

Table 2**Cardiac Structure and Function**

	Controls (n=71)	Non-obese HFpEF (n=96)	Obese HFpEF (n=99)	P value
<i>LV structure & function</i>				
LV diastolic dimension (mm)	47±5	47±5	49±5 [*] †	0.0005
LV end diastolic volume (ml)	104±24	103±26	116±26 [*] †	0.0006
LV end diastolic volume index (ml/m ²)	57±12	56±13	53±11	0.1
LV mass (g)	151±38	166±49	205±54 [*] †	<0.0001
LV mass index (g/m ^{2.7})	37±9	41±12	51±13 [*] †	<0.0001
LV mass/LVEDV (g/ml)	1.5±0.3	1.6±0.4 [*]	1.8±0.3 [*] †	<0.0001
LV ejection fraction (%)	63±4	63±6	63±6	1.0
Mitral E-wave, cm/sec	74±24	91±34 [*]	89±30 [*]	0.001
Mitral annular e' (cm/sec)	8±2	7±2 [*]	7±2	0.004
E/e' ratio	9 (7,11)	13 (10,17) [*]	12 (9,15) [*]	<0.0001
Longitudinal strain (%)	-17±3	-15±4 [*]	-15±4 [*]	0.006
<i>RV structure & function</i>				
RV basal dimension (mm)	30±6	31±6	34±7 [*] †	0.0005
RV mid cavity dimension (mm)	23±5	24±5	27±6 [*] †	0.0003
RV longitudinal dimension (mm)	61±7	61±7	66±7 [*] †	<0.0001
RV fractional area change (%)	52±7	49±9	48±9 [*]	0.02
<i>Pericardial & Ventricular Interaction</i>				
Total epicardial heart volume (ml)	632(517,768)	797(643,979) [*]	945(831,1105) [*] †	<0.0001
Epicardial fat thickness (mm)	6±2	7±2 [*]	10±2 [*] †	<0.0001
Eccentricity index end-diastole	0.97±0.10	0.97±0.08	1.09±0.15 [*] †	<0.0001
Eccentricity index end-systole	0.97±0.12	0.99±0.06	1.10±0.19 [*] †	<0.0001
Ideal/actual radius end-diastole	1.04±0.26	1.05±0.12	1.33±0.39 [*] †	<0.0001
Ideal/actual radius end-systole	1.07±0.29	1.04±0.14	1.32±0.50 [*] †	<0.0001

Data are mean ± SD, median (interquartile range), or n (%). Final column reflects overall group differences.

^{*}
p<0.05 vs controls

†
p<0.05 vs non-obese HFpEF.

LV, left ventricular; EDV, end-diastolic volume; RV, right ventricular.

Table 3**Invasive Hemodynamics at Rest and during Exercise**

	Controls (n=71)	Non-obese HFpEF (n=96)	Obese HFpEF (n=99)	P value
<u>Rest</u>				
<i>Vital signs</i>				
Heart rate (bpm)	64±13	65±13	64±12	0.9
Systolic BP (mmHg)	143±27	152±30	148±31	0.3
Mean BP (mmHg)	97±15	102±17	99±18	0.4
<i>Central pressures</i>				
RA pressure (mmHg)	4±2	8±3 *	11±5 *†	<0.0001
PA systolic pressure (mmHg)	29±8	40±12 *	41±13 *	<0.0001
PA mean pressure (mmHg)	16±4	26±8 *	27±8 *	<0.0001
PCWP (mmHg)	8±3	15±5 *	17±6 *†	<0.0001
RAP/PCWP ratio	0.53±0.20	0.56±0.19	0.64±0.17 *†	0.0004
LVTMP (mmHg)	4±2	7±4 *	6±4 *	<0.0001
LV Stiffness β (/ml)	5.5±0.2	5.7±0.2 *	5.7±0.2 *	<0.0001
V ₃₀ index (ml/m ²)	85±21	75±18 *	73±18 *	0.0003
<i>Vascular function</i>				
EaI (mmHg * m ² /ml)	3.2±1.1	3.7±1.5	3.4±1.1	0.2
SVRI (dyne * m ² /sec * cm ⁵)	2918±925	3053±1094	2789±800	0.3
TACI (ml/mmHg * m ²)	0.6±0.3	0.5±0.2	0.6±0.3	0.2
PVRI (dyne * m ² /sec * cm ⁵)	268±116	338±168 *	338±173 *	0.007
PACI (ml/mmHg * m ²)	2.2±0.8	1.9±0.9	2.0±1.1	0.1
<i>Flow measures and Oxygen Consumption</i>				
Cardiac index (l/min * m ²)	2.7±0.7	2.6±0.6	2.6±0.6	0.7
O ₂ consumption index (ml/min * kg)	2.8±0.5	2.8±0.6	2.2±0.4 *†	<0.0001
AV O ₂ difference (ml/dl)	4.3±0.8	4.6±0.9	4.5±0.8	0.1
<u>Exercise</u>				
<i>Vital signs</i>				
Heart rate (bpm)	106±24	99±23	97±19 *	0.04
Systolic BP (mmHg)	173±33	174±40	191±32 *†	0.006
Mean BP (mmHg)	110±18	114±21	120±20 *	0.02
<i>Central pressures</i>				
RA pressure (mmHg)	8±4	17±6 *	21±7 *†	<0.0001

	Controls (n=71)	Non-obese HFpEF (n=96)	Obese HFpEF (n=99)	P value
PASP (mmHg)	44±13	61±16 *	70±15 *†	<0.0001
PA mean pressure (mmHg)	27±8	43±10 *	49±10 *†	<0.0001
PCWP (mmHg)	15±5	30±5 *	33±7 *†	<0.0001
RAP/PCWP ratio	0.53±0.3	0.55±0.2	0.64±0.22 *†	0.02
LVTMP (mmHg)	7±4	14±6 *	13±8 *	<0.0001
Vascular function				
EaI (mmHg * m ² /ml)	3.5±1.4	4.2±1.9	4.1±1.3	0.07
SVRI (dyne * m ² /sec * cm ⁵)	1634±510	2070±782 *	1941±498	0.01
TACI (ml/mmHg * m ²)	0.6±0.4	0.5±0.5	0.4±0.3	0.2
PVRI (dyne * m ² /sec * cm ⁵)	210±135	311±268	357±320 *	0.01
PACI (ml/mmHg * m ²)	2.0±1.8	1.3±0.8 *	1.1±0.4 *	<0.0001
Flow measures and Oxygen consumption				
Cardiac index (l/min * m ²)	5.3±1.6	4.2±1.3 *	4.3±1.3 *	<0.0001
Oxygen consumption (ml/min * kg)	12.9±4.0	10.0±3.4 *	7.7±2.3 *†	<0.0001
Arterial-venous O ₂ difference (ml/dl)	10.3±2.0	10.0±2.1	9.6±2.0	0.1

Data are mean ± SD, median (interquartile range), or n (%). Final column reflects overall group differences.

* p<0.05 vs controls

† p<0.05 vs non-obese HFpEF.

BP, blood pressure; Ea, effective arterial elastance; LV, left ventricular; LVTMP, left ventricular transmural pressure; PA, pulmonary artery; PCWP, pulmonary capillary wedge pressure; PVRI, pulmonary vascular resistance index; RA, right atrial; RV, right ventricular; and SVRI, systemic vascular resistance index; V₃₀, left ventricular end-diastolic volume at PCWP 30mmHg.