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

BACKGROUND: Heart failure (HF) with preserved ejection fraction (HfPEF) is a heterogeneous syndrome. Phenotyping patients into pathophysiologically homogeneous groups may enable better targeting of treatment. Obesity is common in HfPEF and has many cardiovascular effects, suggesting that it may be a viable candidate for phenotyping. We compared cardiovascular structure, function, and reserve capacity in subjects with obese HfPEF, those with nonobese HfPEF, and control subjects.

METHODS: Subjects with obese HfPEF (body mass index ≥35 kg/m²; n=99), nonobese HfPEF (body mass index <30 kg/m²; n=96), and nonobese control subjects free of HF (n=71) underwent detailed clinical assessment, echocardiography, and invasive hemodynamic exercise testing.

RESULTS: Compared with both subjects with nonobese HfPEF and control subjects, subjects with obese HfPEF displayed increased plasma volume (3907 mL [3563–4333 mL] versus 2772 mL [2555–3133 mL], and 2680 mL [2380–3006 mL]; P<0.0001), more concentric left ventricular remodeling, greater right ventricular dilatation (base, 34±7 versus 31±6 and 30±6 mm, P=0.0005; length, 66±7 versus 61±7 and 61±7 mm, P<0.0001), more right ventricular dysfunction, increased epicardial fat thickness (10±2 versus 7±2 and 6±2 mm; P<0.0001), and greater total epicardial heart volume (945 mL [831–1105 mL] versus 797 mL [643–979 mL] and 632 mL [517–768 mL]; P<0.0001), despite lower N-terminal pro-B-type natriuretic peptide 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 nonobese HfPEF (r≥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-sided heart filling pressures (0.64±0.17 versus 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 versus 0.99±0.06 and 0.97±0.12; P<0.0001). Interdependence was enhanced as pulmonary artery pressure load increased (P for interaction <0.05). Compared with those with nonobese HfPEF and control subjects, obese patients with HfPEF displayed worse exercise capacity (peak oxygen consumption, 7.7±2.3 versus 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.

CONCLUSIONS: Obesity-related HfPEF is a genuine form of cardiac failure and a clinically relevant phenotype that may require specific treatments.
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 the prognosis of people with HFpEF, but phenotyping patients into pathophysiologically homogeneous 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, which 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 compared with nonobese HFpEF and control subjects without HF.

**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 ≥50%, and directly measured elevation in left-sided heart filling pressures (pulmonary capillary wedge pressure [PCWP]) at rest (>15 mm Hg) and/or with exercise (≥25 mm Hg). Subjects with reduced EF (EF <50%), isolated right-sided HF, valvular heart disease (greater than moderate left-sided regurgitation, greater than mild stenosis), unstable coronary disease or recent revascularization, constrictive pericarditis, high-output HF, or cardiomyopathy were excluded. To investigate the characteristics of obesity in HFpEF, we categorized participants according to body mass index (BMI). Nonobese HFpEF was defined by BMI <30 kg/m\(^2\), and obese HFpEF was defined by the presence of class II or greater obesity (BMI ≥35 kg/m\(^2\)). We excluded patients with class I obesity (BMI, 30–34.9 kg/m\(^2\)) to maximize phenotypic differences associated with greater body mass. As a separate control, we also compared obese and nonobese patients with HFpEF and nonobese control subjects (BMI <30 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 and take responsibility for the integrity of the data.

**Clinical Assessment**
Clinical history, laboratory data, and current medications were abstracted from the medical records. Ideal body weight was calculated from height: \(a+bx(\text{height in cm}−150), \text{where } a=48 \text{ for men and } 45 \text{ for women and } b=1.1 \text{ for men and } 0.9 \text{ for women.}^7\) Plasma volume was estimated as follows: \((1−\text{hematocrit})(a+bx \text{weight in kg}), \text{where } a=1530 \text{ for men and } 864 \text{ for women and } b=41 \text{ for men and } 47.9 \text{ for women.}^8\)

**Assessment of Cardiac Structure and Function**
Two-dimensional, M-mode, Doppler, and tissue Doppler echocardiography was performed within 4 weeks of catheterization according to the American Society of Echocardiography guidelines.\(^9\) Echocardiographic measurements were performed retrospectively by an experienced investigator (M.O.) in a blinded fashion. Left ventricular (LV) mass was indexed to height\(^2,7,10\). Myocardial deformation analyses were performed offline with commercially available software (Syngo, Siemens Medical Solutions, Munich, Germany). LV longitudinal strain was measured from 2 apical views as previously described.\(^11,12\) Strain values represent the mean of 3 beats.
Right ventricular (RV) basal, midcavity, and longitudinal dimensions were measured at end diastole with 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. \(^1\) Total epicardial volume was estimated from 2 hemi-ellipsoids containing both atria and ventricles with the apical 4-chamber view. \(^4\) Epicardial fat thickness was measured on the free wall of the RV at end systole as previously described. \(^5\)

**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-sided 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 with 2 methods as shown in Figure I in the online-only Data Supplement. \(^3\),\(^1\) The LV diameter bisecting and perpendicular to the interventricular septum (septolateral dimension) was measured in the parasternal short-axis view, along with the diameter 90° orthogonal to the septolateral dimension in the anteroposterior dimension. The eccentricity index was then calculated as anteroposterior/septolateral dimension. 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 (Figure I in the online-only Data Supplement). An idealized radius was calculated from the planimetered area assuming the LV to be perfectly circular \((R_{\text{ideal}}=\sqrt{A/\pi})\). Actual LV radius was defined as length from the center of the LV cavity to the septum \((R_{\text{actual}})\). The center of the LV was defined by the perpendicular bisector of the septolateral and anteroposterior dimensions. The ratio of \(R_{\text{ideal}}/R_{\text{actual}}\) exceeding unity indicate greater septal shifting toward the LV cavity and enhanced interdependence (Figure I in the online-only Data Supplement).

**Catheterization Protocol**

Patients were studied on their long-term medications in the fasted state after minimal sedation in the supine position as previously described. \(^17\),\(^18\) Right heart catheterization was performed through a 9F sheath via the right internal jugular vein. Pressures in the right atrium (RA) and pulmonary artery (PA) pressures and PCWP were measured at end expiration (mean of ≥3 beats). LV transmural pressure, which reflects LV preload independent of right heart filling pressure and pericardial restraint, was estimated as PCWP−RA pressure. \(^2\),\(^2\)

After baseline hemodynamic assessment, subjects underwent maximal effort invasive exercise assessment. The first stage exercise at 20-W exercise was performed for 5 minutes, and this was followed by 10- to 20-W increments in workload (3-minute stages) to subject-reported exhaustion. Pressure tracings were digitized and stored for offline analysis by an investigator with experience in invasive hemodynamic assessment (B.A.B.).

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

Pulmonary and systemic vascular function was assessed by pulmonary vascular resistance index \((PVR=[\text{mean PA−PCWP}/\text{CI}],\text{ PA compliance index (PACI}=SVI/\text{PA pulse pressure}],\text{ systemic vascular resistance index (SVR}=[\text{mean arterial blood pressure−RA}]×79.9/\text{CI}],\text{ total arterial compliance index (TACI}= SVI/\text{systemic pulse pressure}],\text{ and effective arterial elastance index (Eal}=[0.9×\text{systolic blood pressure}/\text{SVI}])\).

The relationship between LV end-diastolic pressure (EDP) and end-diastolic volume (EDV) \((EDP=\alpha EDV)\) was assessed with invasive PCWP and echocardiographic LV volumes according to the single-beat method of Klotz et al. \(^2\) This analysis yields the LV stiffness constant \((\beta)\), which increases with elevations in LV chamber stiffness, and a predicted LVEDV of 30 mm Hg \((V_{\beta})\), which decreases as diastolic LV chamber capacitance decreases.

**Statistical Analysis**

Data are reported as mean (SD), median (interquartile range), or number (percent) unless otherwise specified. Between-group differences were compared by 1-way ANOVA, Kruskal-Wallis test, or \(\chi^2\) test, as appropriate. The Tukey honestly-significant-difference test or Steel-Dwass test was used to adjust for multiple testing. Linear and nonlinear regressions were used to assess associations between 2 variables. Linear regression models with an interaction term were performed to test the difference in the relationship between dependent and independent variables between 2 groups. For nonnormally 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 nonobese 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 subject with obese HFpEF compared with nonobese HFpEF and control subjects. Compared with control subjects, patients with HFpEF displayed higher prevalence of comorbidities and were treated with HF medicines more frequently. Diabetes mellitus and sleep apnea were more prevalent in obesity-related HFpEF, whereas atrial fibrillation was more common in nonobese HF-
pEF. Hemoglobin and estimated glomerular filtration rate were lower and N-terminal pro-B-type natriuretic peptide (NT-proBNP) was higher in the HFpEF groups compared with control subjects, but natriuretic peptide levels were lower in obese HFpEF compared with non-obese HFpEF (Table 1).

Cardiac Structure and Function

Compared with nonobese HFpEF and control subjects, subjects with obese HFpEF had larger LV dimensions, volumes, and mass, with an increased ratio of LV mass to volume, indicating greater concentric remodeling (Table 2). LV volumes scaled to body surface area in patients with obese HFpEF were not different from those with nonobese HFpEF or control subjects.

Although LV EF was similar in the 3 groups, LV systolic function was impaired in both obese and non-obese HFpEF groups compared with control subjects, evidenced by decreased longitudinal strain (Table 2). Doppler estimates of diastolic function and filling pressures were similarly abnormal in the HFpEF groups compared with control subjects.

RV size was significantly larger in subjects with obese HFpEF compared with both control subjects and subjects with nonobese HFpEF (Table 2). This remained significant after adjustment for the prevalence of sleep apnea (not shown). RV systolic function assessed by fractional area change was depressed in subjects with obese HFpEF compared with control subjects. RV size was directly correlated with body mass (Figure 1A) but not height (not shown).

Resting Hemodynamics and Oxygen Consumption

Compared with subjects with nonobese HFpEF and control subjects, those with obese HFpEF displayed higher RA pressures and PCWP at rest (Table 3). PCWP was directly correlated with NT-proBNP in all patients with

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<tr>
<th>Table 1. Baseline Characteristics</th>
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<tr>
<td>Age, y</td>
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<td>Female, n (%)</td>
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<tr>
<td>eGFR, ml·min⁻¹·1.73 m⁻²</td>
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<tr>
<td>NT-proBNP, pg/mL</td>
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Data are mean±SD, median (interquartile range), or n (%). Final column reflects overall group differences. ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; eGFR, estimated glomerular filtration rate; HFpEF, heart failure with preserved ejection fraction; and NT-proBNP, N-terminal pro-B-type natriuretic peptide.

*P<0.05 versus control subjects.
†P<0.05 versus nonobese HFpEF.
HFpEF, but the relationship was shifted upward in obese HFpEF, meaning that PCWP was higher for any given NT-proBNP value in obese patients with HFpEF (Figure 1C). In contrast, the relationship between NT-proBNP and LV transmural pressure, which more accurately reflects LV distending pressure after accounting for external pericardial constraint, was not different between in obese and nonobese patients with HFpEF (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 nonobese HFpEF.

PA pressures were elevated at rest in obese and nonobese patients with HFpEF owing to high PCWP and higher PVRI (Table 3). In contrast, SVRI, Eal, and systemic and pulmonary arterial compliances were similar in the HFpEF and control groups at rest (Table 3). VO2 index to body weight was lower in subjects with obese HFpEF compared with control subjects and nonobese HFpEF, suggesting a lower proportion of metabolically active tissue. Resting AVO2diff was similar in the 3 groups.

Exercise Capacity and Hemodynamics

Peak exercise workload achieved was lower in subjects with obese HFpEF and nonobese HFpEF compared with control subjects (36±17 and 39±19 versus 69±29 W; P<0.0001). This was related to the limited ability to augment cardiac output with exercise, which was similarly impaired in obese and nonobese HFpEF (Figure 3A). The efficiency of translating metabolic work (∆V02) to external ergometric work (cycling Watts) was lower in subjects with obese HFpEF compared with both nonobese HFpEF and control subjects (Figure 3B). This led to a lower peak VO2 in those with obese HFpEF compared with both patients with nonobese HFpEF and control subjects (Table 3). Peak VO2 achieved during exercise testing was inversely correlated with body weight (Figure 3C). There were no group differ-

### Table 2. Cardiac Structure and Function

<table>
<thead>
<tr>
<th></th>
<th>Control Subjects (n=71)</th>
<th>Patients With Nonobese HFpEF (n=96)</th>
<th>Patients With Obese HFpEF (n=99)</th>
<th>P Value</th>
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<tr>
<td><strong>LV structure and function</strong></td>
<td></td>
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<tr>
<td>LV diastolic dimension, mm</td>
<td>47±5</td>
<td>47±5</td>
<td>49±5**†</td>
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<td>LV end-diastolic volume, mL</td>
<td>104±24</td>
<td>103±26</td>
<td>116±26**†</td>
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<td>LV mass index, mL/m²</td>
<td>57±12</td>
<td>56±13</td>
<td>53±11</td>
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<td>LV mass, g</td>
<td>151±38</td>
<td>166±49</td>
<td>205±54**†</td>
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<td>LV mass index, g/m²</td>
<td>37±9</td>
<td>41±12</td>
<td>51±13**†</td>
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<td>LV mass/LVEDV, g/mL</td>
<td>1.5±0.3</td>
<td>1.6±0.4*</td>
<td>1.8±0.3**†</td>
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<td>LVEF, %</td>
<td>63±4</td>
<td>63±6</td>
<td>63±6</td>
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<tr>
<td>Mitral E wave, cm/s</td>
<td>74±24</td>
<td>91±34*</td>
<td>89±30*</td>
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<tr>
<td>Mitral annular e’, cm/s</td>
<td>8±2</td>
<td>7±2*</td>
<td>7±2</td>
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<td>E/e’ ratio</td>
<td>9 (7–11)</td>
<td>13 (10–17)*</td>
<td>12 (9–15)*</td>
<td>&lt;0.0001</td>
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<tr>
<td>Longitudinal strain, %</td>
<td>−17±3</td>
<td>−15±4*</td>
<td>−15±4*</td>
<td>0.006</td>
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<td><strong>RV structure and function</strong></td>
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<tr>
<td>RV basal dimension, mm</td>
<td>30±6</td>
<td>31±6</td>
<td>34±7**†</td>
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<td>RV mid cavity dimension, mm</td>
<td>23±5</td>
<td>24±5</td>
<td>27±6**†</td>
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<td>RV longitudinal dimension, mm</td>
<td>61±7</td>
<td>61±7</td>
<td>66±7**†</td>
<td>&lt;0.0001</td>
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<tr>
<td>RV fractional area change, %</td>
<td>52±7</td>
<td>49±9</td>
<td>48±9*</td>
<td>0.02</td>
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<td><strong>Pericardial and ventricular interaction</strong></td>
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<tr>
<td>Total epicardial heart volume, mL</td>
<td>632 (517–768)</td>
<td>797 (643–979)*</td>
<td>945 (831–1105)**†</td>
<td>&lt;0.0001</td>
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<tr>
<td>Epicardial fat thickness, mm</td>
<td>6±2</td>
<td>7±2*</td>
<td>10±2**†</td>
<td>&lt;0.0001</td>
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<td>Eccentricity index at end diastole</td>
<td>0.97±0.10</td>
<td>0.97±0.08</td>
<td>1.09±0.15**†</td>
<td>&lt;0.0001</td>
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<td>Eccentricity index at end systole</td>
<td>0.97±0.12</td>
<td>0.99±0.06</td>
<td>1.10±0.19**†</td>
<td>&lt;0.0001</td>
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<td>Ideal/actual radius at end diastole</td>
<td>1.04±0.26</td>
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<tr>
<td>Ideal/actual radius at end systole</td>
<td>1.07±0.29</td>
<td>1.04±0.14</td>
<td>1.32±0.50**†</td>
<td>&lt;0.0001</td>
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Data are means±SD, median (interquartile range), or n (%). Final column reflects overall group differences. EDV indicates end-diastolic volume; EF, ejection fraction; HFpEF, heart failure with preserved ejection fraction; LV, left ventricular; and RV, right ventricular.

*P<0.05 versus control subjects.
†P<0.05 versus nonobese HFpEF.
ences in exercise $\text{AVO}_2$ diff between those with HFpEF and control subjects (Table 3).

With exercise, left and right heart filling pressures were higher in subjects with obese HFpEF compared with both nonobese HFpEF and control subjects (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 and impaired pulmonary vasodilation, manifested by greater decreases in PA compliance and less reduction in PVRI with exertion in obese individuals with HFpEF compared with nonobese individuals with HFpEF and control subjects (Figure 3). Obese patients with HFpEF also displayed more chronotropic incompetence and higher exercise blood pressure compared with control subjects (Table 3).

Myocardial, Pericardial, and Ventricular Interactions

LV diastolic stiffness ($\beta$) was increased and $V_{30}$ indexed to body size was reduced in individuals with both obese and nonobese HFpEF compared with control subjects, in keeping with significant diastolic dysfunction in all patients with HFpEF (Table 3). Epicardial fat thickness was 20% and 50% higher in subjects with obese HFpEF compared with those with nonobese HFpEF and control subjects, respectively (Table 2). The increased epicardial fat thickness, 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 patients with nonobese HFpEF and control subjects (Table 2 and Figures 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 and right and left sides of the heart (ventricular interaction). Compared with both nonobese subjects with HFpEF and control subjects, obese patients with HFpEF 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) and by a higher ratio of RA to PCWP at rest and during exercise (Table 2 and 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 were not simply related to greater RV afterload from pulmonary hypertension (Figure 5). However, the increase in LV eccentricity (and thus interdependence) was amplified to a greater extent in obese patients with HFpEF as RV afterload increases compared with nonobese subjects ($P$ for interaction <0.05 for both; Figure 5).

RA pressure (which approximates pericardial pressure) was greater in obese HFpEF relative to total body $\text{VO}_2$ at rest and during exercise (Figure 5). RA 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 (LV transmural pressure) was increased in those with obese HFpEF compared with subjects with nonobese HFpEF or control subjects (Figure 5).

**DISCUSSION**

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

**Obesity and HFpEF**

Obesity is a major risk factor for HF. Unlike other cardiovascular diseases such as coronary disease and stroke, this excess risk is not explained by traditional risk factors. Increases in body fat cause hemodynamic, metabolic, inflammatory, and hormonal perturbations that stress the heart and vasculature. Recent studies have clearly shown that obesity and weight gain promote abnormalities in myocardial structure and function implicated in the development of HFpEF.

Obesity is highly prevalent in the Western world, and this prevalence is even greater in patients with HFpEF. More than 80% of patients with HFpEF are either overweight or obese, and in a recently reported trial, the average BMI in the patients with HFpEF exceeded 35 kg/m². 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, not cardiac abnormalities, 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 drive cardiac and extracardiac manifestations of disease. A recent series has demonstrated that higher body mass is one of the strongest independent correlates of symptom severity in people with HFpEF, but no study has reported a detailed pathophysiological characterization of the impact of severe obesity among patients with HFpEF.

Pathophysiological 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. Previous studies have reported that subjects with HFpEF may display increased LV diastolic diameter and plasma volume compared with control subjects. 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 compared with those with nonobese HFpEF. The LV in obese HFpEF displayed dilation but also an increase in the ratio of LV mass to volume, indicating that concentric remodeling was present.

Elevation in filling pressures was positively correlated with increased body mass and plasma volume in obese HFpEF but not in nonobese HFpEF (P for interaction=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 patients with HFpEF have unequivocal, objective evidence of cardiac failure that is linked to adiposity and contributes to symptoms. In other words, obese patients with HFpEF 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.

LV diastolic dysfunction is a fundamental mechanism of HFpEF, and we confirm previous studies by showing that diastolic function was impaired in both obese and nonobese subjects compared with control subjects, evidenced by increased chamber stiffness (β) and lower chamber volume at a common PCWP (V_30 index).
addition to LV diastolic dysfunction, we show for the first time that enhanced ventricular interaction plays an important role in obesity-related HFpEF. The increases in chamber volumes, wall thickness, and epicardial fat observed in obese patients with HFpEF 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 obese patients with HFpEF.

The true distending pressure that drives LV filling, or LV transmural pressure, is defined as intracavitary pressure (LV end-diastolic pressure or PCWP) minus the external pressure applied to the LV from the pericardium and right side of the heart.40 Previous studies have demonstrated that pericardial pressure is best approximated by RA pressure,⁴ which was elevated to a greater extent at rest and during exercise in obese patients with HFpEF compared with nonobese patients with HFpEF and control subjects. 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.⁴¹ Each of these changes was observed in the obese patients with HFpEF compared with both nonobese patients with HFpEF and control subjects in the present 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 nonobese HFpEF despite similar LV transmural pressure. This suggests uncoupling between the LV fill-
Impairments in myocardial oxygen utilization with increased epicardial fat, as noted in the present 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 (V̇O₂) 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 patients with HFpEF. 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 Although PA pressures were similar at rest in obese and nonobese HFpEF, there was a greater exercise-induced elevation in PA pressures in obese patients with HFpEF, related to higher PCWP and inadequate pulmonary vasodilation (Figure 3). The causes of this inadequate vasodilation are unclear but could relate to vasoactive adipokines, which 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 as a result of 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 patients with HFpEF as PA pressures rose compared with nonobese HFpEF (Figure 5). This identifies a pathological synergy among 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 pathophysiological observations, these data have a number of potentially important clinical implications. Plasma NT-proBNP levels were correlated with filling pressures in all patients with HFpEF, but the relationship was shifted upward in obese subjects such that for any NT-proBNP level, PCWPs were higher in the presence of obesity (Figure 1C). It is well known that natriuretic peptide levels are lower in obese compared with nonobese patients.51 This has previously been attributed to enhanced natriuretic peptide degradation in fat tissue, alterations in sex hormones,52,53 or insulin resistance.44

Diastolic wall stress is the primary stimulus for BNP 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 nonobese HFpEF, correlations between LV distending pressure (LV transmural pressure) 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: Because 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 have 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 patients with HFpEF displayed more epicardial adipose, it is likely that they were more exposed to cytokines re-
leased 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 in that it functions like a space-occupying lesion in the cardiac fossa that may contribute to the increased 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, in whom this tissue may occupy a substantial proportion of pericardial volume.

Overall, the myriad pathophysiological differences observed between obese and nonobese HFpEF support the notion that the 2 entities should be considered to some extent as subphenotypes, although clearly many interventions will be effective for all patients regardless of the presence or absence of obesity. This may be important for designing optimal treatments, because one of the reasons suggested to explain the failure of prior trials in HFpEF has been related to pathophysiological 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 patients with HFpEF may be better poised to respond to diuretics or other volume-reducing therapies such as sodium-glucose co-transporter 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 kg/m²). Similarly, bariatric surgery has been observed to improve functional capacity in patients with HF with reduced EF. Prospective trials testing weight loss with other behavioral, pharmacological, 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 thus 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 the heart because body surface area increases more than changes in the heart. RV function was assessed with fractional area change only because adequate images for strain imaging or tricuspid annular excursion were not available. The control subjects were 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 be expected only to bias our results toward the null.

Conclusions
Patients with obesity-related HFpEF display unique pathophysiological features, including greater biventricular remodeling, volume overload, more RV 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.

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None.

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FOOTNOTES
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Supplemental Material
Supplementary Figure 1: Schematic representation for determining the eccentricity index and ideal/actual radius ratio. [A] The longest LV diameter bisecting and perpendicular to the interventricular septum (septolateral dimension, SL) was measured in the parasternal short axis view, along with the longest 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. Abbreviations as in Figures 1 and 4.
Supplementary Figure 1: [B] The intersection of SL and AP defined the center of a circle. The area of the LV in the short axis view was measured by planimetry. An idealized radius was then calculated from this area assuming the LV to be perfectly circular ($R_{\text{ideal}} = \sqrt{\text{cavity area}/\pi}$). Actual LV radius was measured from the center to the septum ($R_{\text{actual}}$), and the ratio of $R_{\text{ideal}}$ to $R_{\text{actual}}$ was calculated. Values of $R_{\text{ideal}}/ R_{\text{actual}}$ exceeding unity indicate greater septal shifting toward the LV cavity and enhanced interdependence. Abbreviations as in Figures 1 and 4.