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CLINICAL RESEARCH

Regional Adipose Distribution and its Relationship to Exercise Intolerance in Older Obese Patients Who Have Heart Failure With Preserved Ejection Fraction

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ABSTRACT

OBJECTIVES This study sought to test the hypothesis that older obese patients with heart failure with preserved ejection fraction (HFpEF) have significantly greater abdominal, cardiac, and intermuscular fat than healthy, age-matched controls, out of proportion to total body fat, and that these abnormalities are associated with objective measurements of physical function.

BACKGROUND Recent studies indicate that excess total body adipose tissue contributes to exercise intolerance in patients with HFpEF. However, the impact of the pattern of regional (abdominal, cardiac, intermuscular) adipose deposition on exercise intolerance in patients with HFpEF is unknown.

METHODS We measured total body adiposity (using dual-energy x-ray absorptiometry) and regional adiposity (using cardiac magnetic resonance), peak oxygen uptake (V_{O_2}), 6-min walk distance (6MWD), short physical performance battery (SPPB), and leg press power in 100 older obese patients with HFpEF and 61 healthy controls (HCs) and adjusted for age, sex, race, and body surface area.

RESULTS Peak V_{O_2} (15.7 ± 0.4 ml/kg/min vs. 23.0 ± 0.6 ml/kg/min, respectively; $p < 0.001$), 6MWD (427 ± 7 m vs. 538 ± 10 m, respectively; $p < 0.001$), SPPB (10.3 ± 0.2 vs. 10.9 ± 0.2, respectively; $p < 0.05$), and leg power (117 ± 5 W vs. 152 ± 9 W, respectively; $p = 0.004$) were significantly lower in patients with HFpEF than HCs. Total fat mass, total percent fat, abdominal subcutaneous fat, intra-abdominal fat, and thigh intermuscular fat were significantly higher, whereas epicardial fat was significantly lower in patients with HFpEF than in HC. After we adjusted for total body fat, intra-abdominal fat remained significantly higher, while epicardial fat remained significantly lower in patients with HFpEF. Abdominal subcutaneous fat, thigh subcutaneous fat, and thigh intermuscular fat:skeletal muscle ratio were inversely associated, whereas epicardial fat was directly associated with peak V_{O_2}, 6MWD, SPPB, and leg power. Using multiple stepwise regression, we found intra-abdominal fat was the strongest independent predictor of peak V_{O_2} and 6MWD.

CONCLUSIONS In metabolic obese HFpEF, the pattern of regional adipose deposition may have important adverse consequences beyond total body adiposity. Interventions targeting intra-abdominal and intermuscular fat could potentially improve exercise intolerance. (Exercise Intolerance in Elderly Patients With Diastolic Heart Failure [SECRET]; NCT00959660) (J Am Coll Cardiol HF 2018;6:640–9) © 2018 by the American College of Cardiology Foundation.

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Heart failure with preserved ejection fraction (HFpEF) is the fastest growing form of HF and is associated with high morbidity and mortality (1). Exercise intolerance, manifested as severe exertional dyspnea and fatigue, is a hallmark of chronic HFpEF and is associated with reduced quality of life (2,3). The mechanisms of exercise intolerance are incompletely understood, but it appears that abnormalities in noncardiac, systemic factors are important contributors in addition to cardiac function (3–9).

Obesity is a major independent risk factor for development of HF (10), and >80% of patients with HFpEF are overweight or obese (11,12). Increased adiposity promotes inflammation, hypertension, dyslipidemia, and insulin resistance and impairs cardiac, vascular, pulmonary, and skeletal muscle function, all of which contribute to the pathophysiology of HFpEF (7,12–15). Multiple lines of evidence suggest that excess body adipose tissue contributes to reduced peak exercise oxygen uptake (V_{O_2}) in HFpEF (12,14–16). Adipose-induced inflammation has wide-ranging adverse effects including coronary and systemic microvascular endothelial dysfunction, capillary rarefaction, and impaired skeletal muscle mitochondrial function and protein synthesis that result in reduced skeletal muscle oxygen delivery and extraction (7,9,14,16). Emerging data suggest that, in addition to the amount of total body adipose tissue, the specific location of adipose tissue may play a role in adverse outcomes, including exercise intolerance (4,14,17,18). However, the impact of adipose distribution on exercise performance has not been systematically examined in HFpEF.

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We aimed to test the hypothesis that older obese patients with HFpEF have significantly greater abdominal, cardiac, and intermuscular fat than age-matched healthy controls (HCs), out of proportion to total body fat, and that these abnormalities are associated with objective measurements of physical function. Therefore, we performed a prospective study in patients with HFpEF and HCs, using dual-energy x-ray absorptiometry (DEXA) to assess total body adipose mass and cardiac magnetic resonance (CMR) to determine regional adipose mass, and cardiopulmonary exercise testing (6-min walk distance [6MWD]), and lower extremity muscle power to comprehensively assess physical function.

METHODS

STUDY PARTICIPANTS. As previously described (13), patients were interviewed and examined by a board-certified cardiologist and met these inclusion criteria: ≥60 years of age; body mass index ≥30 kg/m^2; signs and symptoms of HF, as defined by National Health and Nutrition Examination Survey score of ≥3 (19), using criteria by Rich et al. (20), or both; left ventricular (LV) EF ≥50%; no segmental wall motion abnormalities; and no significant ischemic or valvular heart disease, pulmonary disease, anemia, or other disorder that could explain the patients' symptoms (2,21,22). HCs were recruited from the community and excluded if they had any chronic medical illness, were taking any chronic medication, had current complaints or an abnormal physical examination findings (including blood pressure ≥140/90 mm Hg), had abnormal results on the screening tests (echocardiogram, electrocardiogram, cardiopulmonary exercise testing), or regularly undertook vigorous exercise (2,22). The study was approved by the Wake Forest School of Medicine Institutional Review Board. All participants provided written informed consent.

OUTCOME MEASUREMENTS. Outcomes were assessed and images were analyzed by individuals blinded to the participant group.

LV MORPHOLOGY AND FUNCTION. As previously described, LV mass and volumes were assessed by CMR (1.5-T scanner, Siemens Avanto, Tarrytown, New York) from a series of multislice, multiphase gradient-echo sequences positioned perpendicularly to the LV long axis, spanning apex to base (13). The epi- and endocardial borders of each slice were traced manually at end-diastole and end-systole, and volumes were calculated by using Simpson's rule (23). LV

ABBREVIATIONS AND ACRONYMS

6MWD = 6-min walk distance
CMR = cardiac magnetic resonance
DEXA = dual energy x-ray absorptiometry
EF = ejection fraction
HC = age-matched healthy control
HF = heart failure
HFpEF = heart failure with preserved ejection fraction
HFrEF = heart failure with reduced ejection fraction
IMF = intermuscular fat
LV = left ventricle
NYHA = New York Heart Association
SCF = subcutaneous fat
SM = skeletal muscle
SPPB = short physical performance battery
TC = thigh compartment
VAT = ventilatory anaerobic threshold
V_{O_2} = oxygen consumption

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stroke volume and EF were calculated from standard formulae (13).

As previously described, LV filling patterns, mitral annulus velocity, and pulse-wave velocity were assessed by using Doppler echocardiography (iE33 ultrasonography machine, Philips, Eindhoven, the Netherlands) (13).

BODY COMPOSITION. Total body fat and lean mass were measured by using DEXA (Delphi QDR, Hologic Inc.), using standardized protocols as previously described (3,4,13).

Regional scans of the thigh, abdomen, and heart were performed by CMR as previously described (4,13,24). Images were transferred to a dedicated workstation and analyzed using commercially available software (Sliceomatic, Tomovision, Montreal, Quebec, Canada) as previously described (4,13,24). Cross-sections of thigh areas of skeletal muscle (SM), subcutaneous fat (SCF), intermuscular fat (IMF), and bone were measured with images taken at a constant location of the mid-thigh of the left leg. Total thigh area was calculated as the sum of SCF, IMF, SM and bone, and thigh compartment (TC) area was calculated as the sum of SM, IMF, and bone. Abdominal images were taken from the tenth thoracic vertebra to the second sacral vertebra, positioned every 3 cm to cover the entire abdomen. A single slice at the level of the second lumbar vertebra was used to determine abdominal fat measurements, including SCF and intraperitoneal and retroperitoneal fat. Intra-abdominal fat was calculated as the sum of intraperitoneal and retroperitoneal fat. For epicardial (within the pericardium) and paracardial (outside the pericardium) fat volumes, axial images were acquired from the diaphragm to the aortic arch, using a prospective electrocardiographic-gated, T1-weighted, breath-held, black-blood, single-shot, turbo-spin echo sequence. Pericardial fat was calculated by summing epicardial and paracardial fat (24).

PHYSICAL FUNCTION. As previously described, cardiopulmonary exercise testing was performed with the participant on a treadmill, using the modified Naughton (HFpEF) or modified Bruce (HC) protocol, using standardized instructions and encouragement to achieve a peak symptom-limited exhaustive effort (13,25). Continuous expired gas analysis was performed during exercise and averaged over 15-s intervals (Medgraphics Ultima, Medical Graphics Corp., St. Paul, Minnesota) (2,13,25). Peak V_{O_2} was calculated as the average of the last 30 s during peak exercise (2,13,25). Ventilatory anaerobic threshold (VAT) and ventilation and carbon dioxide output ($VE:V_{CO_2}$) slope was assessed as previously described (21,25).

TABLE 1 Patient Characteristics

	HFpEF (n = 100)	HC (n = 61)	p Value
Age, yrs	66.5 ± 5.2	69.3 ± 7.4	0.011
Women	81 (81)	38 (62)	0.010
Whites	55 (55)	58 (95)	<0.001
Weight, kg	105.5 ± 17.9	74.5 ± 16.4	<0.001
Body mass index, kg/m^2	39.3 ± 6.1	25.9 ± 4.9	<0.001
Body surface area, m^2	2.1 ± 0.2	1.8 ± 0.2	<0.001
NYHA functional class			
II	60 (60)	-	-
III	40 (40)	-	-
Ejection fraction, %	61.1 ± 6.0	59.0 ± 4.8	0.030
LV mass, g	214 ± 60	129 ± 35	<0.001
LV mass index, g/m^2*	102 ± 25	70 ± 14	<0.001
Relative wall thickness	0.57 ± 0.12	0.38 ± 0.05	<0.001
Left atrial diameter, cm	4.0 ± 0.5	3.4 ± 0.6	<0.001
Diastolic filling pattern†			
Normal	2 (2)	48 (80)	<0.001
Impaired relaxation	87 (87)	12 (20)	
Pseudonormal	9 (9)	0 (0)	
Restrictive	1 (1)	0 (0)	
Indeterminate	0 (0)	0 (0)	
e′, cm/s	6.2 ± 1.5	7.9 ± 1.6	<0.001
E/e′ ratio	13.1 ± 3.7	9.3 ± 2.2	<0.001
History of atrial fibrillation	3 (3)	-	-
History of established CAD	11 (11)	-	-
History of hypertension	95 (95)	-	-
History of diabetes mellitus	35 (35)	-	-
Blood pressure, mm Hg			
Systolic	135 ± 14	123 ± 11	<0.001
Diastolic	78 ± 8	75 ± 7	0.018
Medications			
Diuretics	76 (76)	-	-
ARBs	35 (35)	-	-
ACE inhibitors	37 (37)	-	-
Beta-blockers	40 (40)	-	-
Ca^{2+} channel blockers	35 (35)	-	-
Nitrates	9 (9)	-	-

Values are mean ± SD or n (%). *LV mass was indexed to body surface area. †Diastolic filling pattern was determined according to American Society of Echocardiography criteria.

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; CAD = coronary artery disease; e′ = early mitral annulus velocity (septal); E = E-wave velocity; HC = healthy control; HFpEF = heart failure with preserved ejection fraction; LV = left ventricle; NYHA = New York Heart Association.

6MWD was assessed as described by Guyatt et al. (26). The short physical performance battery (SPPB) is a validated, reliable measurement of physical function in older populations and is strongly predictive of disability, hospitalization, nursing home readmission, and death (27,28). The battery consists of 3 subtasks: standing balance, 4-m walking speed at usual pace, and time to rise from a chair 5 times (27). Leg press power (W) was assessed using the Nottingham power machine (University of Nottingham, Nottingham, United Kingdom) (13). Leg power

TABLE 2 Exercise Performance Measurements

	Unadjusted Mean ± SD			Adjusted LS Mean ± SE*		
	HFpEF	HC	p Value	HFpEF	HC	p Value
Peak Vo_2						
ml/min	1,509 ± 313	1,852 ± 608	<0.001	1,464 ± 35	1,927 ± 48	<0.001
ml/kg/min	14.5 ± 2.6	25.0 ± 7.0	<0.001	15.7 ± 0.4	23.0 ± 0.6	<0.001
ml/kg lean/min†	27.7 ± 5.2	37.4 ± 7.6	<0.001	28.3 ± 0.7	36.6 ± 0.9	<0.001
ml/kg leg lean/min†	87.4 ± 17.9	117.8 ± 24.1	<0.001	90.9 ± 2.3	112.3 ± 3.0	<0.001
Peak carbon dioxide production, ml/min	1,701 ± 403	2,123 ± 712	<0.001	1,650 ± 43	2,207 ± 60	<0.001
Peak respiratory exchange ratio	1.12 ± 0.08	1.15 ± 0.09	0.073	1.12 ± 0.01	1.15 ± 0.01	0.18
Ventilatory anaerobic threshold, ml/min	1,014 ± 244	1,115 ± 373	0.063	956 ± 25	1,210 ± 35	<0.001
Ventilation/carbon dioxide slope	29.45 ± 3.99	28.56 ± 3.57	0.16	30.11 ± 0.41	27.46 ± 0.57	0.001
Peak heart rate, beats/min	139 ± 18	153 ± 13	<0.001	139 ± 2	153 ± 3	<0.001
Peak systolic blood pressure, mm Hg	177 ± 18	179 ± 18	0.39	176 ± 2	182 ± 3	0.13
Peak diastolic blood pressure, mm Hg	78 ± 9	76 ± 8	0.13	77 ± 1	78 ± 1	0.62
6-min walk distance, m	412 ± 73	563 ± 70	<0.001	427 ± 7	538 ± 10	<0.001
SPPB total score	10.0 ± 1.7	11.3 ± 0.8	<0.001	10.3 ± 0.2	10.9 ± 0.2	0.044
SPPB balance score	3.8 ± 0.6	4.0 ± 0.2	0.010	3.8 ± 0.1	4.0 ± 0.1	0.15
SPPB gait speed score	3.8 ± 0.5	4.0 ± 0.0	<0.001	3.8 ± 0.0	3.9 ± 0.1	0.30
SPPB chair rise score	2.5 ± 1.2	3.3 ± 0.7	<0.001	2.6 ± 0.1	3.0 ± 0.2	0.12
Leg press power, W	112 ± 53	163 ± 67	<0.001	117 ± 5	152 ± 9	0.004
Leg muscle quality, W/cm^2‡	0.91 ± 0.33	1.45 ± 0.52	<0.001	0.97 ± 0.05	1.28 ± 0.08	0.004

*Adjusted for age, race, sex, and body surface area and presented as least square (LS) mean ± SE. †kg of lean body mass and kg of leg lean mass were measured by dual energy x-ray absorptiometry. ‡Leg muscle quality is leg power divided by thigh muscle area.
SPPB = short physical performance battery; other abbreviations as in Table 1.

was chosen due to its strong correlation with disability and other adverse outcomes with aging (29). Muscle quality was calculated as leg power divided by thigh muscle area from the CMR scans (13).

STATISTICAL ANALYSIS. All analyses were performed using SAS Enterprise Guide version 7.1 software (SAS Institute, Arlington, Virginia). All outcomes were tested at the 5% 2-sided level of significance. Patient characteristics are presented as mean ± SD or frequency and percent. Comparisons of patient characteristics were made by independent sample Student's *t*-tests for continuous variables and Fisher exact or chi-square test for categorical variables. Outcome measurement are presented as unadjusted (mean ± SD) and were adjusted (least squares mean ± SE), with a p value for each. Unadjusted values were compared using independent sample Student's *t* tests, whereas adjusted values were compared using analysis of covariance with age, sex, race, and body surface area as covariates; a supplemental analysis was adjusted for total body fat. Associations between regional fat and physical function measurements were made by using Spearman correlations and adjusted for body surface area. Multiple linear regression models were constructed to predict physical function by using stepwise selection with age, sex, and race forced into the model as these are potential confounders in predicting physical function. The following regional fat measures showing consistent significance in bivariate analyses were included as candidate variables in the stepwise selection process: abdominal SCF, intra-abdominal fat, thigh IMF, and epicardial fat. Effect sizes were reported as partial R^2 values.

RESULTS

PARTICIPANTS' CHARACTERISTICS. Clinical characteristics of the patients with HFpEF and HCs are shown in Table 1. Patients with HFpEF were clinically stable New York Heart Association (NYHA) functional class II/III and had typical characteristics of HFpEF, including female preponderance, increased body mass index, increased LV mass and concentric remodeling, increased left atrial size, and Doppler diastolic dysfunction with increased E:e′ ratio.

EXERCISE PERFORMANCE MEASUREMENTS. Peak exercise Vo_2 (ml/min; indexed to either body weight, lean body mass, or leg lean mass), carbon dioxide production, and heart rate were significantly lower in HFpEF than HC participants, whereas ventilation and carbon dioxide slope was significantly higher (Table 2). Peak exercise respiratory exchange ratio (an objective, reliable measurement of participant

TABLE 3 Total and Regional Body Composition Measurements

	Unadjusted Mean ± SD			Adjusted LS Mean ± SE*		
	HFpEF	HC	p Value	HFpEF	HC	p Value
DEXA						
Total mass, kg	102.4 ± 14.2	75.7 ± 16.3	<0.001	94.4 ± 0.6	88.0 ± 0.8	<0.001
Total fat mass, kg	46.7 ± 10.2	24.1 ± 9.4	<0.001	41.0 ± 0.7	32.9 ± 0.9	<0.001
Total percent fat	45.5 ± 6.4	31.5 ± 8.5	<0.001	42.8 ± 0.6	35.6 ± 0.8	<0.001
Total lean mass, kg	53.3 ± 9.1	49.3 ± 11.0	0.016	51.1 ± 0.4	52.8 ± 0.6	0.041
Total percent lean	52.2 ± 6.3	65.5 ± 8.2	<0.001	54.7 ± 0.6	61.6 ± 0.8	<0.001
Cardiac magnetic resonance						
Abdominal SC fat, cm^2	377.8 ± 145.2	147.7 ± 84.5	<0.001	312.9 ± 12.8	236.9 ± 15.9	0.002
Intra-peritoneal fat, cm^2	116.4 ± 61.5	68.8 ± 60.4	<0.001	110.0 ± 6.4	77.7 ± 8.0	0.007
Retroperitoneal fat, cm^2	94.4 ± 51.3	47.3 ± 35.0	<0.001	95.8 ± 4.1	45.4 ± 5.1	<0.001
Intra-abdominal fat, cm^2	210.8 ± 107.9	116.1 ± 90.0	<0.001	205.7 ± 9.7	123.1 ± 12.1	<0.001
Abdominal SC fat:intra-abdominal fat ratio	2.34 ± 1.73	1.91 ± 1.31	0.10	1.94 ± 0.18	2.46 ± 0.22	0.11
Total thigh area, cm^2	316.8 ± 80.4	205.3 ± 47.3	<0.001	277.0 ± 5.6	270.7 ± 7.7	0.56
Thigh SC fat, cm^2	165.2 ± 74.8	73.8 ± 41.9	<0.001	132.9 ± 5.4	126.7 ± 7.5	0.55
TC area, cm^2	151.6 ± 28.7	131.5 ± 32.1	<0.001	144.1 ± 2.1	143.9 ± 3.0	0.96
Femur, cm^2	4.3 ± 0.7	5.9 ± 1.0	<0.001	4.2 ± 0.1	6.1 ± 0.1	<0.001
Thigh IMF, cm^2	25.9 ± 9.2	14.4 ± 5.9	<0.001	23.2 ± 0.9	18.9 ± 1.2	0.014
Thigh IMF:TC, %	17.1 ± 5.2	11.3 ± 4.8	<0.001	16.2 ± 0.6	12.9 ± 0.8	0.003
Thigh SM, cm^2	121.5 ± 25.7	111.2 ± 30.5	0.029	116.8 ± 2.0	118.9 ± 2.8	0.58
Thigh SM:TC, %	80.0 ± 5.1	84.0 ± 5.0	<0.001	80.9 ± 0.6	82.6 ± 0.8	0.11
Thigh IMF:SM ratio	0.22 ± 0.08	0.14 ± 0.07	<0.001	0.21 ± 0.01	0.16 ± 0.01	0.009
Paracardial fat, cm^3	63.1 ± 39.6	53.9 ± 36.7	0.19	63.6 ± 4.1	53.1 ± 5.5	0.18
Epicardial fat, cm^3	36.0 ± 17.7	54.9 ± 20.6	<0.001	36.3 ± 2.3	54.5 ± 3.0	<0.001
Pericardial fat, cm^3	99.0 ± 53.0	108.8 ± 52.9	0.31	99.8 ± 5.6	107.6 ± 7.6	0.48

*Adjusted for age, race, sex, and body surface area and presented as least square (LS) mean ± SE.
DEXA = dual energy x-ray absorptiometry; Fat = paracardial fat + epicardial fat; intra-abdominal fat = intra-peritoneal + retroperitoneal fat; MF = intermuscular fat; pericardial SC fat = subcutaneous fat; SM = skeletal muscle; TC area = SM + IMF + femur; TC area = thigh compartment; Total thigh area = TC area + thigh SC fat.

effort) values in HFpEF participants were similiar to those in HCs. There were no significant differences in peak exercise systolic or diastolic blood pressure (Table 2). The 6MWD, SPPB total score, and leg press power (absolute or indexed to thigh muscle area) were also significantly lower in patients with HFpEF than in HCs (Table 3).

TOTAL AND REGIONAL BODY COMPOSITION MEASUREMENTS. By using DEXA, we found total body mass, total body fat mass, and percent fat to be significantly higher, whereas total lean (muscle) mass and percent lean mass were significantly lower in HFpEF than HC participants (Table 3). According to CMR scans, the following patterns of regional fat deposition were observed in HFpEF versus HC (Table 3): abdominal SCF and intra-abdominal fat were significantly higher, respectively; thigh IMF, thigh IMF:thigh compartment (TC%), thigh IMF:SM ratio were significantly higher, respectively, whereas thigh SCF was similar; and epicardial fat was 33% lower ($p < 0.001$), whereas pericardial and paracardial fat were similar, respectively. Even when adjusted for total body fat, intra-abdominal fat remained significantly higher, whereas epicardial fat remained significantly lower in HFpEF participants than in HCs; additionally, abdominal SCF:intra-abdominal fat ratio became significantly lower in patients with HFpEF than in patients with HC. Furthermore, there was a significant association between intra-abdominal fat and epicardial fat in the patients with HFpEF ($r = 0.37$; $p = 0.001$) but not in HCs ($r = 0.16$; $p = 0.26$).

RELATIONSHIPS AMONG BODY COMPOSITION, EXERCISE TOLERANCE, AND PHYSICAL FUNCTION. All measurements of physical function were inversely related to abdominal and thigh SCF, thigh IMF, thigh IMF:TC (%), and thigh IMF:SM ratio, and positively related to thigh SM:TC (%) and epicardial fat (Tables 4 and 5, Figure 1). Peak Vo_2 showed trends ($p < 0.10$) for inverse relationships with intraperitoneal, retroperitoneal, and intra-abdominal fat. When adjusted for total body fat, peak Vo_2 (ml/min and ml/kg/min), ventilatory anaerobic threshold, and leg press power remained positively related to epicardial fat.

Multiple linear regression with age, sex, and race forced in showed that intra-abdominal fat was the strongest independent predictor of peak Vo_2 and 6MWD, with partial R^2 value of 0.36 for peak Vo_2 and

TABLE 4 Relationships of Cardiac Fat, Abdominal Fat, and Thigh Composition With Peak Vo_2

	Peak Vo_2, ml/min		Peak Vo_2, ml/kg/min		Peak Vo_2, ml/kg lean/min		Peak Vo_2, ml/kg leg lean/min	
	Corr.	p Value	Corr.	p Value	Corr.	p Value	Corr.	p Value
Abdominal SCF, cm^2	−0.60	<0.001	−0.73	<0.001	−0.36	<0.001	−0.35	<0.001
Intra-peritoneal fat, cm^2	−0.12	0.19	−0.13	0.17	−0.16	0.073	−0.08	0.38
Retroperitoneal fat, cm^2	−0.15	0.10	−0.21	0.024	−0.30	<0.001	−0.19	0.036
Intra-abdominal fat, cm^2	−0.13	0.15	−0.15	0.091	−0.24	0.010	−0.13	0.15
Thigh SCF, cm^2	−0.63	<0.001	−0.71	<0.001	−0.34	<0.001	−0.39	<0.001
Thigh IMF, cm^2	−0.46	<0.001	−0.59	<0.001	−0.39	<0.001	−0.39	<0.001
Thigh IMF:TC, %	−0.57	<0.001	−0.66	<0.001	−0.40	<0.001	−0.40	<0.001
Thigh SM, cm^2	0.51	<0.001	0.46	<0.001	0.19	0.034	0.20	0.026
Thigh SM:TC, %	0.54	<0.001	0.62	<0.001	0.35	<0.001	0.36	<0.001
Thigh IMF:SM ratio	−0.57	<0.001	−0.66	<0.001	−0.39	<0.001	−0.39	<0.001
Paracardial fat, cm^3	0.00	0.96	0.04	0.65	−0.06	0.50	0.03	0.72
Epicardial fat, cm^3	0.36	<0.001	0.43	<0.001	0.28	0.002	0.32	<0.001
Pericardial fat, cm^3	0.17	0.060	0.23	0.013	0.10	0.28	0.18	0.050

Corr. = Spearman correlation coefficient; other abbreviations as in Tables 2 and 3.

0.2 for 6MWD, respectively (Table 6), whereas abdominal subcutaneous and epicardial fat remained significant but modest predictors (inverse for epicardial).

DISCUSSION

Multiple recent studies have shown that excess total body adipose tissue is a key contributor to the severely reduced peak Vo_2 in the metabolic:obese HFpEF phenotype (3,4,8,9,15). Prior studies in other disorders suggest that the location of excess adipose tissue has effects independent of total body adiposity and that regional adiposity may be an important determinant of impaired cardiac function and exercise intolerance (12,14,15,24). However, the impact of regional adiposity in HFpEF is unknown. In this study, we examined the distribution of adipose tissue in patients with HFpEF compared to that in HCs and the relationships of regional adipose depots with multiple objective measurements of exercise tolerance and physical function. The major new findings from this study include the fact that older, obese patients with HFpEF have relatively larger depots of abdominal and thigh adipose and smaller amounts of epicardial fat than HCs. There was also a significant association between intra-abdominal fat and epicardial fat in patients with HFpEF but not in HCs. Additional novel findings are that abdominal SCF, thigh SCF, and the thigh IMF:SM ratio were inversely associated with all objective measurements of physical function, including peak Vo_2, 6MWD, ventilatory anaerobic threshold, SPPB, and leg power, whereas epicardial fat was directly associated with these physical function measures. In multiple linear regression, intra-abdominal fat yielded the highest partial R^2 value among all regional fat measurements and was the strongest independent predictor of peak Vo_2 and 6MWD. These data suggest that, in HFpEF, the pattern of regional adipose distribution may have important adverse consequences beyond those of total body adipose tissue.

Previous studies in other disorders showed that increased abdominal fat is associated with concentric remodeling, LV diastolic dysfunction, and adverse subclinical changes in LV mechanics (30–34). Obokata et al. (15) recently reported that, compared to non-obese patients with HFpEF and controls, obese patients with HFpEF had more concentric LV remodeling, greater right ventricular dysfunction, increased right and left heart filling pressures, impaired pulmonary vasodilation, and reduced peak Vo_2 during maximal supine cycle exercise. We confirmed and significantly extended these findings by showing, in a relatively large cohort of older, obese patients with HFpEF compared to HC, that obese patients with HFpEF have increased left atrial size, LV mass, and relative wall thickness and impaired Doppler measurements of diastolic function, as well as impairments in multiple objective measures of physical function, including peak Vo_2, VAT, SPPB, and leg muscle power, and by examining the relationships of physical function with multiple measures of total and regional adipose using both DEXA and CMR.

Increased adiposity promotes inflammation, hypertension, dyslipidemia, and insulin resistance, all of which contribute to the pathophysiology of HFpEF (13,16). Moreover, adipose-induced inflammation has

TABLE 5 Relationships of Cardiac Fat, Abdominal Fat, and Thigh Composition With Other Exercise Performance Measurements

	Ventilatory Anaerobic Threshold, ml/min		6-Min Walk Distance, m		Total SPPB Score		Leg Press Power, W	
	Corr.	p Value	Corr.	p Value	Corr.	p Value	Corr.	p Value
Abdominal SCF, cm^2	−0.39	<0.001	−0.56	<0.001	−0.33	<0.001	−0.67	<0.001
Intra-peritoneal fat, cm^2	−0.00	0.97	−0.12	0.23	−0.03	0.78	0.05	0.60
Retroperitoneal fat, cm^2	−0.08	0.40	−0.19	0.054	−0.08	0.43	0.07	0.51
Intra-abdominal fat, cm^2	−0.02	0.80	−0.15	0.13	−0.04	0.65	0.08	0.41
Thigh SCF, cm^2	−0.42	<0.001	−0.58	<0.001	−0.38	<0.001	−0.63	<0.001
Thigh IMF, cm^2	−0.29	0.001	−0.46	<0.001	−0.33	<0.001	−0.36	<0.001
Thigh IMF:TC, %	−0.37	<0.001	−0.54	<0.001	−0.40	<0.001	−0.49	<0.001
Thigh SM, cm^2	0.35	<0.001	0.39	<0.001	0.41	<0.001	0.57	<0.001
Thigh SM:TC, %	0.35	<0.001	0.50	<0.001	0.40	<0.001	0.48	<0.001
Thigh IMF:SM ratio	−0.37	<0.001	−0.54	<0.001	−0.40	<0.001	−0.50	<0.001
Paracardial fat, cm^3	0.00	0.97	−0.02	0.84	0.01	0.94	0.15	0.12
Epicardial fat, cm^3	0.27	0.002	0.36	<0.001	0.21	0.034	0.43	<0.001
Pericardial fat, cm^3	0.13	0.16	0.16	0.12	0.09	0.39	0.30	0.002

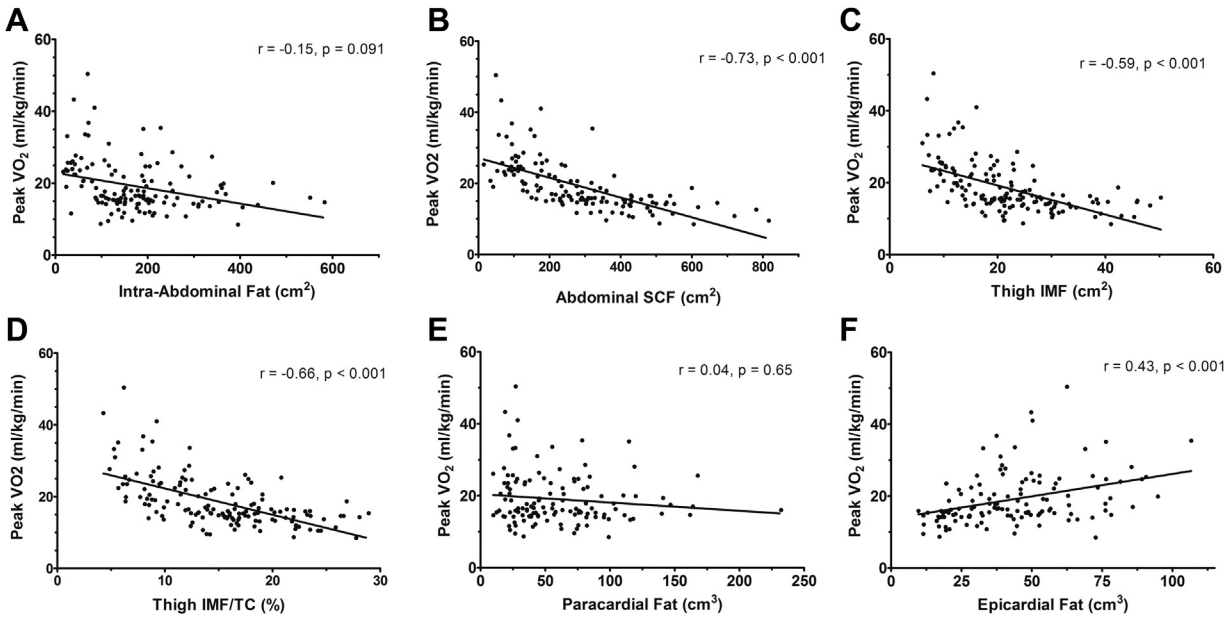
Data were adjusted for body surface area and are Spearman correlation coefficients. p Values indicate significance for each correlation for the overall sample (HFpEF and HC).
IMF = intermuscular fat; Intra-abdominal fat = intra-peritoneal + retroperitoneal fat; Pericardial fat = pericardial fat + epicardial fat; SCF = subcutaneous fat; SPPB = short physical performance battery; SM = skeletal muscle; TC = thigh compartment.

wide-ranging adverse effects including coronary and systemic microvascular endothelial dysfunction, capillary rarefaction and impaired skeletal muscle mitochondrial function, and protein synthesis that results in reduced skeletal muscle oxygen delivery and use (7,9,14). A consequence of adipose-mediated inflammatory endothelial dysfunction and capillary rarefaction is that it reduces O_2 delivery to the active muscles, resulting in fatigue even during low-level exercise (7,14,22). Indeed, a novel finding from our study was that excess abdominal adipose tissue was inversely associated with peak Vo_2, VAT, 6MWD, and leg muscle power. Taken together, these data suggest that central adiposity may be an important contributor to the impaired exercise tolerance and physical function in older, obese patients with HFpEF.

In addition to multiple novel findings, our results confirm, in a much larger group of subjects, our prior reports that increased thigh IMF area and IMF:SM ratio are significantly related to severely reduced peak Vo_2 in older, obese patients with HFpEF (3,4), suggesting that abnormal skeletal muscle composition and its adverse consequences contribute to exercise intolerance in HFpEF (35,36). We extended these findings by demonstrating that increased thigh SCF, IMF, IMF:TC ratio, and thigh IMF:SM ratio were associated with other objective measurements of impaired physical function, including lower VAT, SPPB, 6MWD, and leg power. The mechanisms whereby increased thigh IMF are associated with increased anaerobic metabolism during submaximal exercise may be related to the deleterious effect excess adiposity has on skeletal muscle mitochondrial function. Specifically, Bharadwaj et al. (37) reported that thigh fat volume, thigh SCF and thigh IMF were negatively associated with skeletal muscle citrate synthase activity in sedentary older individuals. Moreover, we previously reported that older patients with HFpEF with obesity have decreased skeletal muscle oxidative fibers, enzymes, capillarity, and mitochondrial function that result in decreased diffusive O_2 transport and impaired peak and reserve oxygen use by the active muscles (4,7-9,22,38), confirming findings reported in an animal model of HFpEF (38).

In contrast to our pre-specified hypothesis, we found that epicardial fat, even when adjusted for body surface area or for total body fat, was substantially (33%) lower in HFpEF than in HC participants. However, these results are consistent with multiple prior studies in patients with HF with reduced EF (HFrEF), which showed significantly reduced epicardial fat (39,40). They differ, however, from the study by Obokata et al. (15) who reported finding greater epicardial fat thickness in nonobese and obese HFpEF participants than in controls. The discrepancy among studies may be due to the techniques used to quantify epicardial fat. Obokata et al. (15) used echocardiography to measure 1-dimensional thickness of epicardial fat at a single point adjacent to the right ventricular free wall. We used CMR to acquire volumetric measurements of epicardial and paracardial fat around the entire heart (41). Adipose tissue provides an extremely high signal-to-noise ratio for CMR, whereas with echocardiography, it has low signal-to-noise ratio. Furthermore, adipose tissue slows

FIGURE 1 Peak Vo_2 (ml/kg/min) Vs. Regional Fat Measures



Regression plots for baseline measures of peak Vo_2 (ml/kg/min) versus **(A)** intra-abdominal fat, **(B)** abdominal SCF, **(C)** thigh IMF, **(D)** thigh IMF as percent of TC, **(E)** paracardial fat, **(F)** epicardial fat. Similar results were found for nonindexed peak Vo_2 (ml/min) as well. Regional fat measurements were obtained using cardiac resonance imaging. Thigh compartment was calculated as intermuscular fat + skeletal muscle + bone. Spearman *r* and p values were included for reference. IMF:TC = intermuscular fat:thigh compartment; SCF = subcutaneous fat; TC = thigh compartment.

ultrasound transmission speed, potentially overestimating thickness measurements, and can cause refraction of ultrasound waves. Furthermore, echocardiography overestimates epicardial fat and underestimates paracardial fat compared to CMR (42), likely due to difficulty in distinguishing the pericardium. Finally, volumetric measurements by CMR are not only more accurate and reproducible than by echocardiography, they preclude systematic errors from measuring epicardial fat thickness at a single point that are due to individual differences in epicardial fat distribution, such as occurs in HF patients from redistribution of epicardial fat due to LV remodeling (41,43).

While our study does not address the potential mechanism(s) for reduced epicardial fat observed in obese patients with HFpEF, prior studies in HFrEF have highlighted the fact that epicardial fat plays a major role in regulating fatty acids to cardiac muscle as a local energy source and that the heart can switch fuel sources in response to stress (44). For example, in the setting of obesity and diabetes, myocardial fatty acid β-oxidation increases at the expense of glucose use (45). Given the high prevalence of impaired glucose tolerance in metabolic:obese HFpEF, it seems possible that increased reliance on fatty acid β-oxidation may, at least partly, explain the observed reduction in epicardial fat in HFpEF (and in prior studies of HFrEF) patients compared to HCs.

In contrast to abdominal and thigh fat, which were inversely related to physical function, epicardial adipose was directly associated with all physical function measures, and remained a significant, independent, positive predictor of physical function even after adjusting for total body fat. This suggests that, unlike abdominal and thigh fat, epicardial

TABLE 6 Predictors of Physical Function*

	Peak Vo_2, ml/kg/min		6-Min Walk Distance, m		Leg Press Power, W	
	Partial R^2	p Value	Partial R^2	p Value	Partial R^2	p Value
Age	0.140	<0.001	0.156	<0.001	0.053	0.021
Sex	0.355	<0.001	0.093	<0.001	0.293	<0.001
Race	0.086	0.001	0.005	0.43	0.015	0.23
Intra-abdominal fat	0.358	0.003	0.200	<0.001	-	-
Abdominal SCF	0.077	<0.001	0.182	<0.001	0.075	0.006
Epicardial fat	0.034	0.046	0.033	0.048	-	-

*Age, sex, race forced into model; thigh intermuscular fat did not reach significance for peak Vo_2 or 6-min walk distance.
Vo_2 = oxygen consumption; other abbreviations as in Table 5.

adipose tissue may not adversely impact physical function in HFpEF. This would be consistent with data regarding epicardial fat and myocardial energy utilization discussed above.

The finding of a significant association between intra-abdominal fat and epicardial fat in the HFpEF patients but not in the HCs further supports the validity of our key finding that obese patients with HFpEF may have a unique pattern of regional fat distribution.

CLINICAL IMPLICATIONS. Reducing total body adiposity through bariatric surgery can prevent incident HF and improve exercise intolerance in established HFrEF (12,13). Our data suggest that, in obese:metabolic HFpEF, in addition to reducing total fat mass, additional benefit may be realized by targeting specific fat depots, such as intra-abdominal and intermuscular adipose depots. Indeed, dietary weight loss significantly improved symptoms, exercise capacity, and quality-of-life in older obese patients with HFpEF, and these benefits were related to improved body and regional composition, including reduced fat mass and improved thigh muscle mass:intermuscular fat ratio.

STUDY LIMITATIONS. Our study has several strengths, including prospective design, relatively large numbers of HFpEF and HCs, comprehensive measures of body composition by both DEXA and CMR, and multiple objective measures of physical function. Our study also has potential limitations. Although DEXA can potentially overestimate fat and lean mass in the presence of edema, our patients with HFpEF were well compensated without overt fluid overload. Moreover, our CMR assessments confirmed and extended our DEXA results by demonstrating regional differences in fat distribution between HFpEF and HC. Average BMI in HCs was lower than that in HFpEF participants, and even though we adjusted for body size, our data do not definitively prove that the pattern of regional fat distribution we identified is specific to obese HFpEF, which would require a control group matched for BMI and comorbidities.

CONCLUSIONS

In patients with the metabolic obese HFpEF phenotype, in addition to total body adipose, the pattern of regional adipose deposition may have important adverse consequences for HFpEF and its primary manifestation, exercise intolerance. Interventions targeting specific adipose depots, such as intra-abdominal and thigh intermuscular fat, have the potential to improve the clinically important outcome of exercise intolerance.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Metabolic obese patients with HFpEF have excess intra-abdominal and intermuscular adipose tissue that is independently related to exercise capacity, beyond total body adipose.

TRANSLATIONAL OUTLOOK: Strategies to differentially impact regional adipose could improve exercise intolerance in metabolic:obese HFpEF.

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