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

Mark J. Haykowsky, PhD,[a] Barbara J. Nicklas, PhD,[b] Peter H. Brubaker, PhD,[e] W. Gregory Hundley, MD,[c] Tina E. Brinkley, PhD,[b] Bharathi Upadhya, MD,[c] J. Thomas Becton, MS,[c] Michael D. Nelson, PhD,[a] Haiying Chen, PhD,[d] Dalane W. Kitzman, MD[b,c]

## 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 $\pm$ 0.4 ml/kg/min vs. 23.0 $\pm$ 0.6 ml/kg/min, respectively; $p < 0.001$), 6MWD (427 $\pm$ 7 m vs. 538 $\pm$ 10 m, respectively; $p < 0.001$), SPPB (10.3 $\pm$ 0.2 vs. 10.9 $\pm$ 0.2, respectively; $p < 0.05$), and leg power (117 $\pm$ 5 W vs. 152 $\pm$ 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;■:■–■) © 2018 by the American College of Cardiology Foundation.

From the [a]College of Nursing and Health Innovation, University of Texas at Arlington, Arlington, Texas; [b]Section on Gerontology and Geriatric Medicine, Department of Internal Medicine, Wake Forest School of Medicine, Wake Forest University, Winston-Salem, North Carolina; [c]Cardiovascular Medicine, Department of Internal Medicine, Wake Forest School of Medicine, Wake Forest University, Winston-Salem, North Carolina; [d]Department of Biostatistical Science, Wake Forest School of Medicine, Wake Forest University, Winston-Salem, North Carolina; and the [e]Department of Exercise and Health Science, Wake Forest School of Medicine, Wake Forest University, Winston-Salem, North Carolina. Supported U.S. National Institutes of Health grants R01AG18917, R01AG045551, R01HL107257, P30-AG21331, and UL1TR001420 (Dr. Kitzman), R15NR016826 (Dr. Haykowsky), K01AG033652 (Dr. Brinkley), and R01HL093713 (Dr. Nicklas). Dr. Kitzman has consulted for Relypsa, Abbvie, GlaxoSmithKline, St. Luke's Medical Center, DCRI, and Corvia Medical; received grants from Novartis and St. Luke's Medical Center; holds the

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**ABBREVIATIONS AND ACRONYMS**

**6MWD** = 6-min walk distance

**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

**CMR** = cardiac magnetic resonance

**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

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.

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 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).

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