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EDITORIAL COMMENT

Weighty Matters in HFpEF and Aging*

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In this issue of *JACC: Heart Failure*, Haykowsky et al. (1) compare older obese adults with heart failure with preserved ejection fraction (HFpEF) with healthy control (HC) subjects, analyzing the impact of body composition on exercise performance as a dimension of the disease. The study employed magnetic resonance imaging to examine regional differences in adiposity and their relations to physical function. Total fat mass, total percent fat, abdominal subcutaneous fat, intra-abdominal fat, and thigh intermuscular fat were higher in HFpEF versus HC subjects. After adjusting for age, gender,

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race, and body surface area, abdominal subcutaneous fat, thigh subcutaneous fat, and thigh intermuscular fat-skeletal muscle ratio were inversely associated with a multiple functional indices (i.e., peak oxygen utilization [Vo_2], 6-min walking distance, the Short Physical Performance Battery, and leg power). Overall, the study corroborates prior work showing that adiposity impacts HFpEF, and also advances the HFpEF field by suggesting that regional differences of adiposity are associated with distinctive functional consequences.

The authors speculate that treatments targeting regional adipose deposits may ultimately prove to be significant therapeutic enhancements for obese HFpEF patients. Such novel reasoning sets these investigators apart from others who have tended to focus on HFpEF and obesity pathophysiology more in terms of local or mechanical burdens on the heart. Obokata et al. (2), for example, also compared peak Vo_2 in obese and nonobese HFpEF patients, and demonstrated lower peak Vo_2 (7.7 ± 2.3 ml/kg/min vs. 10.0 ± 3.4 ml/kg/min) in the obese HFpEF cohort. They attributed these differences in function to increased plasma volume, more concentric left ventricular remodeling, and greater right ventricular dilatation and right ventricular dysfunction. They also showed distinctive hemodynamic characteristics in obese HFpEF patients, suggestive of greater pericardial restraint and heightened ventricular interdependence. Corroborating data showed that for any natriuretic peptide level, obese adults with HFpEF had more severe heart failure than nonobese patients did. Such cardiocentric perspectives infer priority of cardiovascular-oriented therapies to moderate what is conceptualized as load or mechanical pathophysiology. In contrast, in their manuscript, Haykowsky et al. (1) shift the conceptual focus of HFpEF therapy to body composition. These investigators view adiposity itself as the pathophysiological mechanism (i.e., a basis of inflammation, hypertension, dyslipidemia, and insulin resistance) with downstream effects that include microvascular endothelial dysfunction, capillary rarefaction, and impaired skeletal muscle mitochondrial function and protein synthesis.

The value of the Haykowsky et al. (1) paper is reinforced by viewing it as a manifestation of a progression of fundamental scientific insights regarding HFpEF. In the earliest days of HFpEF discovery, it was primarily conceptualized as diastolic filling impairment and to an associated emphasis on putative therapies targeting ventricular lusitropic enhancement. Thereafter, Paulus et al. (3)

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essentially transformed the field by reframing HFpEF pathophysiology as a derivative of inflammation with associated dysregulation of the nitric oxide–cyclic guanosine monophosphate-protein kinase G signaling cascade. With this shift in understanding, Paulus et al. also implicitly underscored the importance of aging biology, sedentariness, and multimorbidity as elemental contributors to HFpEF pathophysiology. More recently, the burgeoning field of geroscience has added to the evolution of insights, and has led to elucidation of molecular mechanisms related to aging that induce cardiovascular changes predisposing to HFpEF (4). Furthermore, geroscience has clearly demonstrated that HFpEF develops as part of broader aging patterns of systemic morphological and physiological changes.

Thus, although this study by Haykowsky et al. (1) stands out as strikingly novel relative to conventional HFpEF literature, especially because cardiocentric therapeutic efforts have not been successful, the conclusions seem less surprising when considered in relation to contemporary geriatric scientific insights. Among geriatric scientists, body composition, physical functional capacity, and faltering health are already recognized as interconnected aspects of aging, with clinical manifestations that include heart failure as well as diabetes, frailty, and other age-related intricacies. Diminished lean mass, increased fat mass, and increased skeletal muscle fat infiltration have all been recognized as fundamental sequelae of aging (5).

Age-related changes in body composition, especially in adults who are sedentary and overfed, predictably predispose to metabolic derangements (particularly insulin resistance), inflammation, and many other aspects of risk. In one pertinent study, Pellegrinelli et al. (6) reported that secreted factors from visceral adipose tissue, but not subcutaneous adipose tissue, decreased muscle protein synthesis and instigated muscle atrophy processes, and repressed pathways of oxidative metabolism. This study elucidates a mechanistic basis for the interaction between muscle and adipose tissue, particularly the relatively greater risks from visceral adipose tissue, and parallels many themes raised by Haykowsky et al. (1).

Other more granular aspects of the Haykowsky et al. (1) study are also important to note. Foremost, only younger subsets of HFpEF patients were studied (66.5 ± 5.2 years of age). Because HFpEF incidence surges in the decades past 65 years of age, when the changes in body composition are likely to accelerate, the focus on only younger subsets of older adults in this study may underestimate the impact of body composition. Also, in Haykowsky et al.'s analysis, obese HFpEF patients were compared with nonobese control subjects. It would have been relatively more meaningful if obese HFpEF patients had been compared with nonobese HFpEF and obese HC subjects. Likewise, expressing cardiorespiratory fitness (peak Vo_2) in units per kilogram body weight is problematic when the denominator (body weight) differs between the groups being compared. Although the investigators take steps to account for differences in body mass index statistically, their ability to make definitive conclusions fundamentally oriented to body composition remains limited. Finally, it stands out that Haykowsky et al. (1) show reduced epicardial fat in the obese HFpEF patients as compared with HC subjects, especially because these findings contrast with those of Obokata et al. (2), and to their assertions that epicardial fat contributes to pericardial constraint and diastolic filling impairments.

Overall, Haykowsky et al. (1) are to be commended for advancing insights regarding body composition and cardiovascular disease, and for melding cardiovascular and geriatric scientific perspectives. Whereas heart disease has traditionally been assessed as if it was principally a cardiovascular problem, Haykowsky et al. (1) showcase a complex holistic perspective. More research is needed to clarify the intricate science of aging and its impact on cardiovascular and other aspects of health, especially given the rapid growth of the older adult demographic and to the age-related vulnerability of these adults to unique pathologies and severe morbid effects.

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REFERENCES

1. Haykowsky MJ, Nicklas BJ, Brubaker PH, et al. Regional adipose distribution and its relationship to exercise intolerance in older obese patients who have heart failure with preserved ejection fraction. J Am Coll Cardiol HF 2018;6:640–9.

2. Obokata M, Reddy YNV, Pislaru S, Melenovsky V, Borlaug BA. Evidence supporting the existence of a distinct obese phenotype of

heart failure with preserved ejection fraction. Circulation 2017;136:6–19.

3. Paulus WJ, Tschöpe C. A novel paradigm for heart failure with preserved ejection fraction: comorbidities drive myocardial dysfunction and remodeling through coronary microvascular endothelial inflammation. J Am Coll Cardiol 2013; 62:263–71.

4. Paneni F, Diaz Cañestro C, Libby P, Lüscher TF, Camici GG. The aging cardiovascular system: understanding it at the cellular and clinical levels. J Am Coll Cardiol 2017;69:1952–67.

5. Delmonico MJ, Harris TB, Visser M, et al. Longitudinal study of muscle strength, quality, and adipose tissue infiltration. Am J Clin Nutr 2009; 90:1579–85.

6. Pellegrinelli V, Rouault C, Rodriguez-Cuenca S, et al. Human adipocytes induce inflammation and atrophy in muscle cells during obesity. Diabetes 2015;64:3121–34.

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