

EDITORIAL COMMENT

Insights From MESA (Multi-Ethnic Study of Atherosclerosis) Into the Crypts of Fat*



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Obesity, particularly visceral adiposity, is increasingly recognized as a major risk factor for heart failure (HF), especially HF with preserved ejection fraction (HFpEF). Besides the established effects of excess weight and visceral adiposity on blood pressure and insulin resistance, obesity also promotes systemic inflammation and renal dysfunction, conditions that have been strongly associated with the development of HFpEF (1). Cohort studies with computed tomography (CT) data have demonstrated that visceral, but not subcutaneous fat predicts HF risk independently of body mass index, and that this risk is not entirely explained by mediators such as hypertension, diabetes, and systemic inflammation. Taken together, this work suggests that fat depots, besides being surrogates for obesity, have additional and heterogeneous properties that modify cardiovascular and HF risk. A growing body of evidence has linked epicardial fat, a component of pericardial fat, with risk of atrial fibrillation in the general population, diastolic dysfunction in various patient populations, and worse hemodynamic profile in patients with prevalent HFpEF. However, to this point, there has been no prospective evidence linking pericardial or epicardial fat with risk of incident HF.

In this issue of the *Journal*, Kenchaiah et al. (2) investigate the association of pericardial fat with incident HF in 6,785 participants of the MESA (Multi-Ethnic Study of Atherosclerosis). In their analyses, higher pericardial fat volume (PFV) measured by CT was associated with a greater risk of incident HF. In adjusted analyses, the hazard ratio per standard deviation of PFV was 1.44 (95% confidence interval [CI]: 1.21 to 1.71; $p < 0.001$) in women and 1.13 (95% CI: 1.01 to 1.27; $p = 0.03$) in men, with a significant ($p = 0.01$) gender-based interaction. When PFV was dichotomized using data-driven cutoffs, high PFV ($\geq 70 \text{ cm}^3$ in women and $\geq 120 \text{ cm}^3$ in men) was associated with a 2-fold greater risk of HF in women and approximately 50% greater risk of HF in men. These associations remained significant after further adjustment for circulating markers of systemic inflammation (C-reactive protein and interleukin 6) and natriuretic peptide levels and were similar across MESA racial subgroups. In further analyses by incident HF subtype, elevated PFV was associated with increased risk of HFpEF but not HF with reduced ejection fraction.

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Importantly, the association between PFV and HF risk was still present after including in the model's data on abdominal subcutaneous and visceral fat in a subset of MESA participants with abdominal CT scans performed a median of 3 years after the baseline examination.

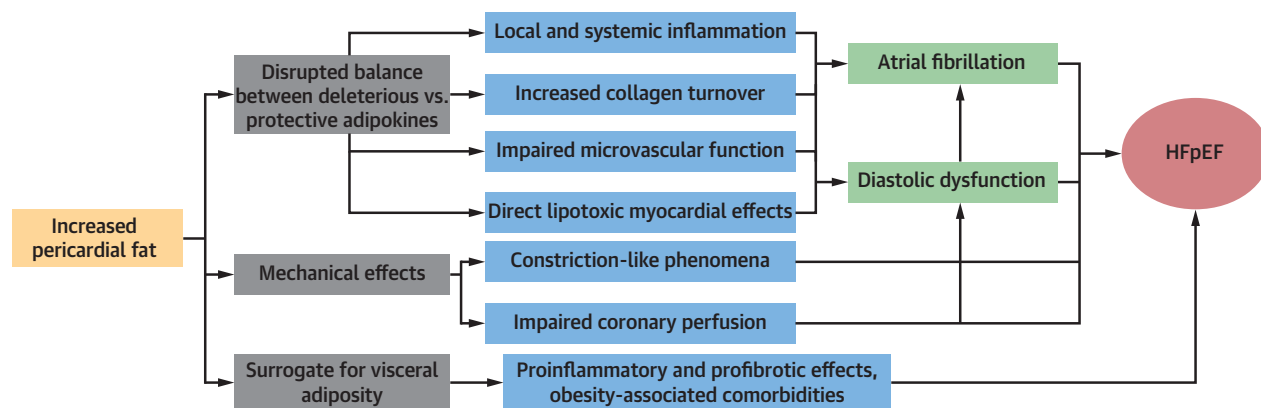
This is the first cohort study demonstrating an epidemiological link between pericardial fat and incident HF. There are a few noteworthy limitations in the study. As the authors note, data on visceral abdominal fat, which has been linked with HF risk, were available only in a subset of patients and were not obtained simultaneously with PFV. Also, Kenchaiah et al. (2) adjusted for hypertension and

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FIGURE 1 Pericardial Fat and Risk for HFpEF



Potential mechanisms underlying the association between increased pericardial fat and HFpEF include: 1) a disrupted balance in adipokines, leading to local and systemic proinflammatory effects, increased collagen turnover, impaired microvascular function, and direct lipotoxic effects, eventually promoting the development of atrial fibrillation and diastolic dysfunction; 2) direct mechanical effects, leading to myocardial constrictive phenomena and impaired coronary perfusion, therefore contributing to diastolic dysfunction; and 3) acting as a proxy for visceral adiposity, obesity-associated comorbidities, and related cardiometabolic effects. HFpEF = heart failure with preserved ejection fraction.

diabetes diagnoses but not for blood pressure, hemoglobin A1c, or duration of these diseases: factors related to visceral adiposity and major contributors to HF risk. Last, the authors assessed epicardial and paracardial fat combined, and these 2 depots may have different effects on cardiac structure and function. Despite these limitations, the work by Kenchaiah et al. (2) highlights the role of fat around the heart as a contributor to HFpEF risk. Several points merit further discussion.

First, the findings by Kenchaiah et al. (2) complement those of a previous MESA study, in which higher PFV (but not hepatic fat) by CT was associated with increased left ventricular (LV) mass, concentric LV remodeling, and incident atherosclerotic cardiovascular disease. Together with previous work, these findings confirm that all fat is not equal. Although recent work has focused on the adverse impact of excess epicardial fat, this fat depot has important physiologic functions also, including mechanical protection of the coronary arteries, fatty acid homeostasis regulation in the coronary microcirculation, supplementation of fatty acids to the myocardium during stress conditions, and secretion of anti-inflammatory cytokines (3). However, excess epicardial fat can shift the physiologic balance toward a proinflammatory and lipotoxic milieu (4), with adverse biologic and mechanical effects on the myocardium (Figure 1).

Second, the propensity of MESA participants with high PFV specifically toward HFpEF adds to data showing strong association of epicardial fat with measures of diastolic dysfunction (5). Lipotoxicity can lead to impaired mitochondrial bioenergetics, oxidative stress, and impaired autophagy, all implicated in the pathogenesis of HFpEF (4). Increased PFV also may exert a physical compressive role. Obese patients with HFpEF and excess epicardial fat have higher LV eccentricity and higher resting and exercise filling pressures, suggesting ventricular interdependence and pericardial restraint (6). Evidence also suggests epicardial fat is associated with the presence, severity, and recurrence of atrial fibrillation (7). In a cohort of obese patients, atrial fibrillation was a major mediator of HFpEF (8). In all, several pathways link increased epicardial fat specifically to HFpEF, offering potential targets for preventive interventions.

Third, the work of Kenchaiah et al. (2) adds to the growing evidence suggesting that epicardial fat has differential effects in men versus women. Women are particularly predisposed to epicardial and intramyocardial fat expansion and adipocyte-mediated inflammation (9,10). In a dobutamine stress study, visceral fat depots, with epicardial fat depot showing the strongest association, were associated with reduced myocardial perfusion in women but not in men (11). Postmenopausal women with atrial

fibrillation have higher peri-atrial adiposity, associated with impaired atrial function (12). These data suggest that adipocyte-mediated myocardial alterations may be particularly relevant for the development of HFpEF in women (9).

What would be the next steps? Can we use epicardial or PFV as a risk stratification tool (primarily for HFpEF) or as a marker for patient selection for interventions, at least in a large-scale research setting initially? These applications require wider availability and standardization of the marker of interest. Echocardiography can measure epicardial fat (thickness), but correlation with epicardial fat volume is modest and the evidence is limited compared with CT measurements. Even with CT, measurement of pericardial and epicardial fat is challenging and time-consuming, as currently there are no standardized protocols. On the positive side, a low-radiation, noncontrast CT protocol (“coronary calcium scan”) can quantify epicardial fat with excellent reproducibility (13). Integration in commercial software is helpful; however, a universal protocol and definition of these fat depots would be a major next step.

Assuming we can overcome challenges with measurement, how can we use this marker to improve patient outcomes? One scenario would be to incorporate a “calcium scan” for PFV in patients at risk for HFpEF, especially women, with the purpose of intensifying control of cardiometabolic risk factors with currently available agents. This approach would

require a clinical pre-screening tool to select patients for PFV CT and prospective validation. Clinical HF risk scores could be applied for this purpose. Another scenario would be using elevated PFV as a target for weight loss interventions and therapy with novel agents that possess favorable cardiometabolic properties, including sodium glucose cotransporter 2 inhibitors and glucagon-like peptide-1 receptor agonists, which have favorable effects on epicardial fat mass (14,15).

In summary, increased pericardial fat is associated with higher risk for incident HFpEF in a large multi-ethnic cohort study. There are several potential mechanisms by which pericardial fat may increase the risk for HFpEF, but further investigation of this complex relationship is needed. Further studies on whether agents with favorable metabolic profile and weight loss interventions modify risk for HFpEF through effects on PFV, powered for sex-specific effects, are warranted.

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REFERENCES

1. Ter Maaten JM, Damman K, Verhaar MC, et al. Connecting heart failure with preserved ejection fraction and renal dysfunction: the role of endothelial dysfunction and inflammation. *Eur J Heart Fail* 2016;18:588-98.
2. Kenchaiah S, Ding J, Carr JJ, et al. Pericardial fat and the risk of heart failure. *J Am Coll Cardiol* 2021;77:2638-52.
3. Rabkin SW. Epicardial fat: properties, function and relationship to obesity. *Obes Rev* 2007;8:253-61.
4. Packer M. Epicardial adipose tissue may mediate deleterious effects of obesity and inflammation on the myocardium. *J Am Coll Cardiol* 2018;71:2360-72.
5. Fitzgibbons TP, Czech MP. Epicardial and perivascular adipose tissues and their influence on cardiovascular disease: basic mechanisms and clinical associations. *J Am Heart Assoc* 2014;3:e000582.
6. Koeppe KE, Obokata M, Reddy YNV, Olson TP, Borlaug BA. Hemodynamic and functional impact of epicardial adipose tissue in heart failure with preserved ejection fraction. *J Am Coll Cardiol HF* 2020;8:657-66.
7. Wong CX, Ganesan AN, Selvanayagam JB. Epicardial fat and atrial fibrillation: current evidence, potential mechanisms, clinical implications, and future directions. *Eur Heart J* 2017;38:1294-302.
8. Jamaly S, Carlsson L, Peltonen M, Andersson-Assarsson JC, Karason K. Heart failure development in obesity: underlying risk factors and mechanistic pathways. *ESC Heart Fail* 2021;8:356-67.
9. Packer M, Lam CSP, Lund LH, Maurer MS, Borlaug BA. Characterization of the inflammatory-metabolic phenotype of heart failure with a preserved ejection fraction: a hypothesis to explain influence of sex on the evolution and potential treatment of the disease. *Eur J Heart Fail* 2020;22:1551-67.
10. Wu CK, Lee JK, Hsu JC, et al. Myocardial adipose deposition and the development of heart failure with preserved ejection fraction. *Eur J Heart Fail* 2020;22:445-54.
11. Hall ME, Brinkley TE, Chughtai H, et al. Adiposity is associated with gender-specific reductions in left ventricular myocardial perfusion during dobutamine stress. *PLoS One* 2016;11:e0146519.
12. Kim JS, Shin SY, Kang JH, et al. Influence of sex on the association between epicardial adipose tissue and left atrial transport function in patients with atrial fibrillation: a multislice computed tomography study. *J Am Heart Assoc* 2017;6:e006077.
13. Bos D, Leening MJG. Leveraging the coronary calcium scan beyond the coronary calcium score. *Eur Radiol* 2018;28:3082-7.
14. Packer M. Drugs that ameliorate epicardial adipose tissue inflammation may have discordant effects in heart failure with a preserved ejection fraction as compared with a reduced ejection fraction. *J Card Fail* 2019;25:986-1003.
15. Lopaschuk GD, Verma S. Mechanisms of cardiovascular benefits of sodium glucose cotransporter 2 (SGLT2) inhibitors: a state-of-the-art review. *J Am Coll Cardiol Basic Transl Sci* 2020;5:632-44.

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