Epicardial fat in heart failure with reduced versus preserved ejection fraction

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Epicardial adipose tissue (EAT) plays important physiological and pathological roles in the regulation of myocardial function. By sharing the same microcirculation as the myocardium, EAT may maintain cardiac health via mechanical, metabolic, thermogenic and paracrine functions[1]; on the other hand, EAT inflammation in obesity may mediate myocardial dysfunction and heart failure (HF).[1] Prior studies reported conflicting associations between EAT and HF (*Table 1*).[2–6] Importantly, the method of measuring EAT may impact results. Magnetic resonance imaging (MRI) allows measurement of whole heart EAT volume or mass, whereas echocardiography only allows measurement of EAT thickness over the free wall of the right ventricle. None of the prior studies included both MRI and echocardiographic measurements of EAT, as well as both HF with preserved (HFpEF) and reduced ejection fraction (HFrEF) compared to controls without HF from the same population.

Magnetic resonance imaging images were available for 457 participants, of whom 93 were excluded due to artefacts on MRI caused by either cardiac surgery or pericardial effusion. Patients could be included as inpatients or outpatients. We compared EAT mass by MRI (EAT_{MRI}) and EAT thickness by echocardiography (EAT_{Echo}) in 251 prospectively recruited patients with a validated diagnosis of HF (18% HFpEF, left ventricular ejection fraction ≥50%) and 113 community-based controls without HF, all of whom underwent simultaneous cardiac MRI and echocardiography by standardized protocol in a nationwide study. Controls without HF were identified from a door-to-door census, and invited to participate. Patients with severe valvular disease, previous cardiac surgery and pericardial effusion leading to artefacts on MRI were excluded. EAT_{MRI} was assessed from a standard short-axis stack of balanced steady-state free precession cine MRI images acquired across the right and left ventricles using CVI42 release 5.9.3 (Circle Cardiovascular Imaging, Calgary, Canada) software. Cardiac volumes, left ventricular mass (LVM) and global longitudinal strain (GLS) were determined by standard MRI methods. Native and post-contrast (15 min post-administration of 0.1 mmol/kg of gadobutrol) myocardial T1 mapping sequences acquired in basal and mid short-axis slices were used to estimate extracellular volume (ECV). Areas of macro-scar were excluded, in keeping with current guidelines.[7] EAT_{Echo} thickness was defined as the echo-free space between myocardium and pericardium layer in the parasternal long or short-axis view on two-dimensional transthoracic echocardiography (GE Healthcare, Milwaukee, WI, USA).

Table 1 Overview of studies on epicardial fat in heart failure with reduced and preserved ejection fraction with major findings

	Study design	Sample size	Method	Major findings
HFpEF				
Obokata *et al.* (2017)[6]	Retrospective, single centre	HFpEF: 195 Controls: 71	Echocardiography: EAT thickness	EAT increased in patients with HFpEF compared to controls
Van Woerden *et al.* (2018)[2]	Prospective, single centre	HFpEF: 64 Controls: 20	MRI: EAT volume	EAT increased in patients with HFpEF compared to controls and related to markers of inflammation
Haykowsky *et al.* (2018)[3]	Prospective, single centre	HFpEF: 100 Controls: 61	MRI: EAT volume	EAT reduced compared to controls and associated with greater peak VO_2 max in HFpEF
HFrEF				
Doesch *et al.* (2010)[4]	Retrospective, single centre	HF: 66 Controls: 32	MRI: EAT volume	EAT and EAT/LVMi ratio reduced compared to controls
HFrEF and HFpEF				
Wu *et al.* (2020)[5]	Prospective, single centre	HFrEF: 34 HFpEF: 164 Controls: 108	MRI: EAT mass	EAT increased in patients with HFrEF and HFpEF compared to controls
Tromp (2021)	Prospective, multicentre	HFrEF: 204 HFpEF: 47 Controls: 113	MRI: EAT mass Echocardiography: EAT thickness	EAT mass increased, but EAT/LVM ratio and EAT thickness reduced in HFrEF and HFpEF Increase in EAT associated with worse functional parameters and markers of fibrosis in HFpEF compared to HFrEF

EAT, epicardial adipose tissue; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LVM, left ventricular mass; LVMi, left ventricular mass index; MRI, magnetic resonance imaging; VO_2, oxygen consumption.

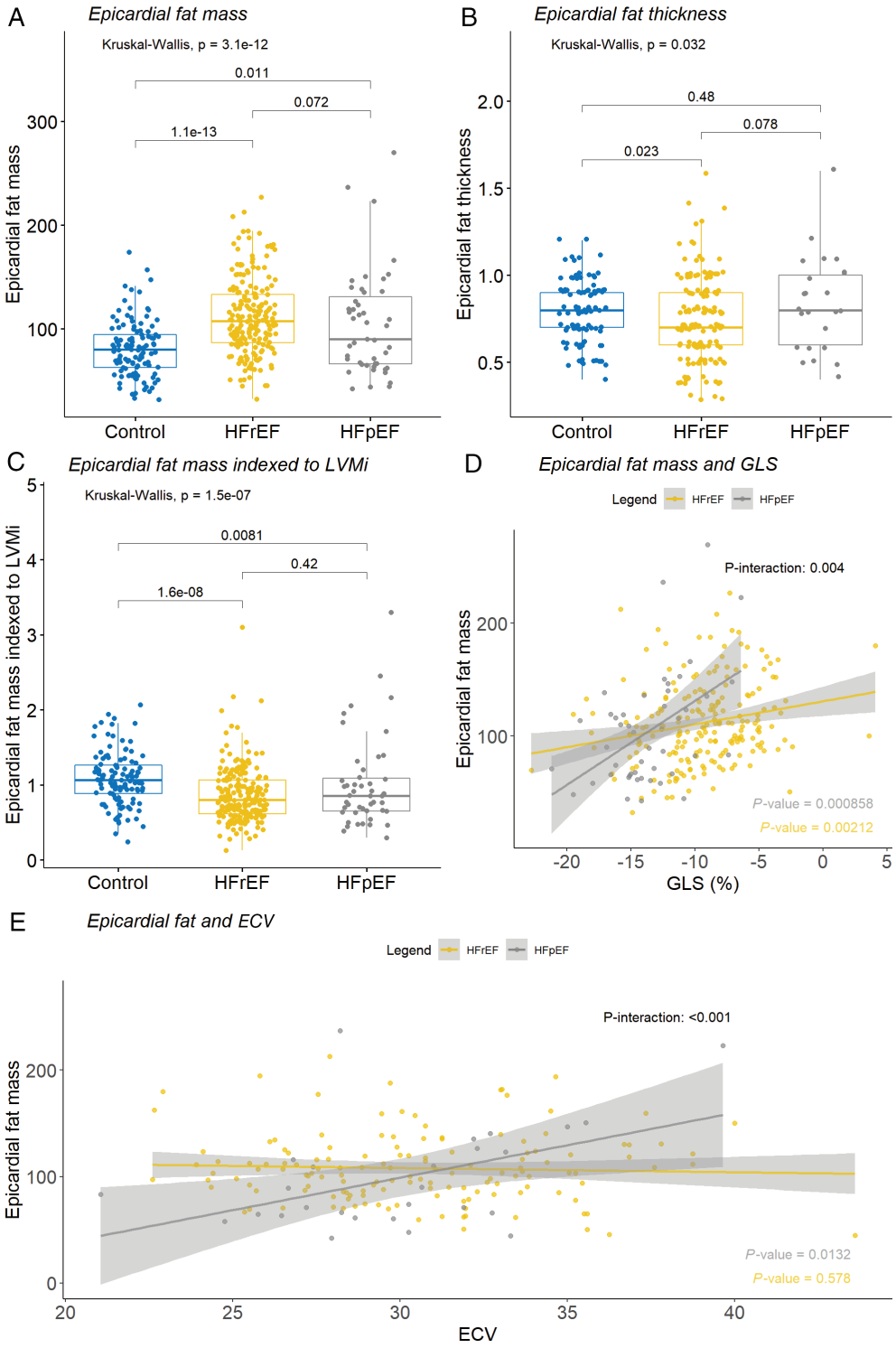

Figure 1 Box plots of (*A*) epicardial fat mass stratified to control ($n = 113$), heart failure with reduced ejection fraction (HFrEF, $n = 204$), and heart failure with preserved ejection fraction (HFpEF, $n = 47$). (*B*) Epicardial fat thickness on echocardiography stratified to control ($n = 103$), HFrEF ($n = 146$), and HFpEF ($n = 24$). (*C*) Epicardial fat mass/left ventricular mass ratio stratified to control ($n = 113$), HFrEF ($n = 204$), and HFpEF ($n = 47$). (*D*) Association of epicardial fat mass with global longitudinal strain (GLS) stratified to HFrEF ($n = 202$) and HFpEF ($n = 47$). (*E*) Association of epicardial fat mass with ECV stratified to HFrEF ($n = 144$) and HFpEF ($n = 27$). ECV, extracellular volume; LVMi, left ventricular mass index.

Differences between groups were tested using the Chi-square test, Kruskal–Wallis test or one-way analysis of variance when appropriate. The association between EAT_{MRI} mass and functional/structural parameters on MRI was tested using linear regression analysis correcting for age, sex, ethnicity, body mass index (BMI), history of diabetes mellitus and atrial fibrillation. All tests were performed two-sided and *P*-values of <0.05 were considered statistically significant. EAT_{MRI} was available in 364 participants, EAT_{Echo} in 273 participants, and ECV in 171 (68%) out of 251 patients. Statistical analyses were performed with STATA 16.0 (Stata Corp, College Station, TX, USA) and R version 4.0.2.

Patients with HFrEF were younger (55 ± 11 years) and patients with HFpEF older (63 ± 12 years) compared to controls (59 ± 10 years, $P < 0.001$). Of the 113 non-HF controls, 44% were men, compared to 82% in HFrEF and 65% in HFpEF ($P < 0.001$). BMI was higher in patients with HFpEF (median 30 kg/m^2) compared to HFrEF (median 26 kg/m^2) and controls (median 24 kg/m^2). Compared to controls, EAT_{MRI} mass was higher in HFpEF and highest in HFrEF (medians 80, 90 and 107 g, respectively; $P < 0.001$; *Figure 1A*). After adjustment for confounders, EAT_{MRI} mass was increased in HFrEF ($P < 0.001$), and similar in HFpEF compared to controls. In contrast, EAT_{Echo} thickness was lowest in HFrEF (median 0.7 cm) compared to controls and HFpEF ($P < 0.03$; *Figure 1B*). To reconcile the discrepancy between EAT_{MRI} mass and EAT_{Echo} thickness results, we indexed EAT_{MRI} mass for heart size, recognizing that a larger heart, with larger epicardial surface, would be expected to have higher overall EAT_{MRI} mass (in contrast to EAT_{Echo} thickness localized at the right ventricular wall). After indexation for LVM, the EAT_{MRI}/LVM_{MRI} ratio was lower in HFpEF and HFrEF compared to controls (*Figure 1C*); this remained significant after multivariable adjustment. In patients with HF, greater EAT_{MRI} mass was associated with worse left ventricular GLS ($\beta = -0.21$, $P = 0.001$). This association was stronger in HFpEF compared to HFrEF (HFpEF: $\beta = -0.48$, $P = 0.003$ vs. HFrEF: $\beta = -0.15$, $P = 0.016$, $P_{interaction} = 0.005$; *Figure 1D*), independent of clinical covariates. After exclusion of outliers for GLS (>0%), the interaction term between HF subtype (HFrEF/HFpEF) and GLS for epicardial fat remained significant. Furthermore, greater EAT_{MRI} mass was associated with higher cardiac ECV in HFpEF ($\beta = 0.63$, $P = 0.034$) but not in HFrEF ($P_{interaction} < 0.001$; *Figure 1E*).

In this prospective study of HFpEF and HFrEF compared to community-based controls, studied with both MRI and echocardiographic measurements of EAT, we found that (i) total EAT_{MRI} mass was increased in HFrEF and HFpEF, while the EAT_{MRI}/LVM_{MRI} ratio and EAT_{Echo} thickness were reduced in HFrEF and HFpEF compared to controls without HF; (ii) increased EAT_{MRI} mass was more strongly associated with left ventricular dysfunction (GLS) and fibrosis (ECV) in HFpEF than HFrEF. Our findings are consistent with some prior reports showing an increase in epicardial fat mass or volume in HFpEF and/or HFrEF compared to controls[2,5,6]; but not others, which show a reduction of epicardial fat in patients with HFpEF.[3,4] We extend on previous findings by including data on EAT thickness on echocardiography; and EAT mass, and ECV on MRI in the same patients. Previous conflicting reports might be explained by differences in inclusion criteria and measurement methods; for instance, Haykowsky *et al.*[3] exclusively included patients with a BMI of ≥ 30 kg/m^2 who may have had obesity-related hypervolaemic HF. In the present study, the reduction in EAT_{MRI}/LVM_{MRI} ratio and EAT_{Echo} thickness, most prominent in HFrEF, suggests possible thinning of the epicardial fat pad out of proportion to the increase in heart size. Indeed, in HFrEF, intramyocardial fat is reduced while being increased in HFpEF compared to controls.[5] EAT, as a depot of white adipocytes rich in energy, can serve as a metabolic reservoir under conditions of increased myocardial energy demand which may become depleted in HF.[8] In contrast, specifically in inflammatory HFpEF, EAT may be a focal source of inflammatory cytokines, causing fibrosis and stiffening of the myocardium leading to functional impairment.[1] Our study provides supportive evidence for this hypothesis in showing a stronger association of increased EAT mass with left ventricular dysfunction and fibrosis in HFpEF than HFrEF. Yet, our cross-sectional design precludes conclusions regarding causality, and our findings warrant validation in future large prospective studies including assessments of both the quality and quantity of EAT. We did not exclude patients with cachexia or thyroid disease, and excluded patients with artefacts on MRI or evidence of pericardial effusion, which might have influenced our results. More men than women consented to participate in our study, leading to possible participation bias.

In conclusion, we provide evidence of EAT thinning despite increase in total EAT mass in HF, most pronounced in HFrEF. Greater total EAT is more closely associated with worse functional parameters and markers of myocardial fibrosis in HFpEF than in HFrEF. These data highlight the possible divergent role(s) of EAT in the pathophysiology of HFrEF and HFpEF.

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