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RESEARCH ARTICLE

Epicardial adipose tissue related to left atrial and ventricular function in heart failure with preserved versus reduced and mildly reduced ejection fraction

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Aim

Different associations between epicardial adipose tissue (EAT) and cardiac function have been suggested in patients with heart failure with preserved (HFpEF) versus reduced and mildly reduced ejection fraction (HFrEF/HFmrEF). However, few studies have directly compared the association between EAT and left atrial (LA) and left ventricular (LV) function in patients with HFpEF and HFrEF/HFmrEF.

Methods and results

We studied EAT thickness using transthoracic echocardiography in a multicentre cohort of 149 community-dwelling controls without heart failure, 99 patients with HFpEF, and 366 patients with HFrEF/HFmrEF. EAT thickness was averaged from parasternal long-axis and short-axis views, respectively, and off-line speckle tracking analysis was performed to quantify LA and LV function. Data were validated in an independent cohort of 626 controls, 243 patients with HFpEF, and 180 patients with HFrEF/HFmrEF. For LV function, LV global longitudinal strain (GLS) was measured in both derivation and validation cohorts. For LA function, LAGLS at reservoir, contractile and conduit phase were measured in the derivation cohort, and only LAGLS at reservoir phase was measured in the validation cohort. In the derivation cohort, EAT thickness was lower in HFrEF/HFmrEF (7.3 ± 2.5 mm) compared to HFpEF (8.3 ± 2.6 mm, $p < 0.05$) and controls (7.9 ± 1.8 mm, $p < 0.05$). Greater EAT thickness was associated with better LV and contractile LA function in HFrEF/HFmrEF, but not in HFpEF (p for interaction <0.05). These findings were confirmed in the validation cohort, where EAT thickness was lower in HFrEF/HFmrEF (6.7 ± 1.4 mm) compared to HFpEF (9.6 ± 2.8 mm; $p < 0.05$) and controls (7.7 ± 2.3 mm; $p < 0.05$). Greater EAT thickness was associated with better LV and reservoir LA function in patients with HFrEF/HFmrEF but worse LV and reservoir LA function in patients with HFpEF (p for interaction <0.05). Thickened EAT (EAT thickness >10 mm) was associated with LA dysfunction (LAGLS at reservoir phase <23%) in HFpEF, but not in HFrEF/HFmrEF.

Conclusion

Epicardial adipose tissue thickness is greater in patients with HFpEF than HFrEF/HFmrEF. Increased EAT thickness is associated with worse LA and LV function in HFpEF but the opposite in HFrEF/HFmrEF.

Keywords Epicardial adipose tissue • HFpEF • HFrEF/HFmrEF • Echocardiography

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Introduction

Accumulating evidence suggests that distinctive pathophysiological processes are involved in the onset and progression of heart failure (HF) with reduced and mildly reduced (HFrEF/HFmrEF) versus preserved ejection fraction (HFpEF).[1–4] Neurohormonal activation is considered one of the primary pathophysiological mechanisms in HFrEF/HFmrEF, which is characterized by left ventricular (LV) systolic dysfunction and cardiac chamber dilatation.[4] Conversely, systemic or local inflammation related to comorbidities, leading to microvascular dysfunction, is one of the important pathophysiological mechanisms of HFpEF, which is characterized by LV diastolic dysfunction, stiffness, and subsequent increase of left atrial (LA) pressure.[1–3]

Epicardial adipose tissue (EAT) shares similar genetic features with brown adipose tissue and is a unique visceral fat exerting both detrimental and protective effects on modulating cardiac function and proposed to play a pathogenic role in the development of HF.[5] The disequilibrium between these detrimental and protective effects of EAT on the myocardium might play different pathophysiological roles in the development and progression of HFpEF versus HFrEF/HFmrEF. Previous studies reported conflicting results about the relationship between EAT and different phenotypes of HF.[6–11] Although recent studies have shown that increased EAT in patients with HFpEF was associated with higher right-sided filling pressures and pulmonary hypertension,[7,8] it remains unknown whether a similar trend of association between EAT and left-sided cardiac function is observed in patients with HFpEF versus HFrEF/HFmrEF.

Therefore, the current study aimed to compare EAT thickness and its association with LA and LV function using echocardiography in two independent cohorts of HFpEF, HFrEF/HFmrEF, and control subjects.

Methods

Study populations

The derivation group consisted of 99 patients with HFpEF and 366 patients with HFrEF/HFmrEF who were recruited from a nationwide, prospective, multicentre, observational HF study from Singapore and 149 control participants without HF.[11] Briefly, patients with HF were either hospitalized with a primary diagnosis of HF or seen as outpatients at a HF management clinic within 6 months of decompensated HF. HFpEF was ascertained by LV ejection fraction (LVEF) ≥50% and HFrEF/HFmrEF by LVEF <50%. Exclusion criteria were patients with severe valve disease as the primary cause of HF, primary diagnosis of acute coronary syndrome causing transient pulmonary oedema, end-stage renal failure or receiving renal replacement therapy, or specific subgroups of HF including constrictive pericarditis, complex adult congenital heart disease, hypertrophic cardiomyopathy, eosinophilic myocarditis, cardiac amyloid, and acute chemotherapy-induced cardiomyopathy.[11] Control participants without HF were enrolled from an ongoing, prospective, population-based cross-sectional study in Singapore using door-to-door census; subjects with coronary artery disease (CAD), valvular heart disease, and previous history of cardiac surgery were excluded.[11] Written informed consent was obtained from each participant. All studies were performed in accordance with guidelines of the Declaration of Helsinki, and study protocols were approved by the Institutional Review Boards.

Validation group

The validation cohort consisted of 243 patients with HFpEF and 180 patients with HFrEF/HFmrEF, and 626 control participants from the MacKay Memorial Hospital, Taipei, Taiwan. Asymptomatic control participants who were willing to participate in cardiovascular health screening survey using echocardiography were recruited from the MacKay Memorial Hospital. Patients with HF were retrospectively included based on the adjudicated medical history of HF between 1 June 2011 and 30 June 2013. HF diagnosis was established on the basis of hospitalization within the past 12 months with HF symptoms (New York Heart Association [NYHA] class II–IV) or signs fulfilling Framingham criteria, and requiring intravenous diuretic therapy, accompanied by elevated natriuretic peptide level (B-type natriuretic peptide [BNP] ≥100 pg/ml, or N-terminal pro-B-type natriuretic peptide [NT-proBNP] ≥300 pg/ml). HFrEF/HFmrEF was defined by LVEF <50%, and HFpEF by LVEF ≥50%. Exclusion criteria for both patients with HF and control participants included the presence of significant and primary valvular heart diseases, idiopathic pulmonary hypertension, isolated right-sided HF from chronic lung disorders or idiopathic pulmonary hypertension, congenital heart disease, diagnosed cardiomyopathies, acute coronary syndrome, and end-stage renal disease (estimated glomerular filtration rate [eGFR] <15 ml/min/1.73 m^2) or ongoing renal replacement therapy.

Echocardiography

Comprehensive transthoracic echocardiography was performed on each participant in both derivation and validation cohorts based on the American Society of Echocardiography guideline[12] by experienced sonographers using Vivid ultrasound systems (GE Healthcare, Chicago, IL, USA). All echocardiographic images were digitally stored and analysed post-offline using EchoPAC software (GE Vingmed Ultrasound, Horten, Norway). In the derivation cohort, LV volume at end-systole (LVESV) and end-diastole (LVEDV) were measured using the biplane Simpson method and LVEF was derived. In the validation cohort, LV end-diastolic (LVEDD) and end-systolic (LVESD) dimensions, interventricular septal (IVS) and LV posterior wall (LVPW) thicknesses were measured in the parasternal long-axis view. LVEDV and LVEF were derived either using the biplane Simpson method or Teichholz M-mode method in the validation cohort. LV mass was calculated using the Devereux formula and LA volume by the area–length method, and indexed for body surface area, respectively, as LV mass index and LA volume index (LAVi). LV diastolic function was assessed using mitral valve early (E) and late (A) diastolic velocity, mean value of early diastolic mitral annular lateral and septal velocity (e′) as well as the ratio of E over mean e′ (E/e′). Two-dimensional speckle tracking echocardiography was performed to obtain LA (LAGLS) and LV global longitudinal strain (LVGLS, reported as the absolute value). LVGLS was obtained and averaged from apical four-, two-, three-chamber views, respectively. LAGLS at the reservoir, contractile and conduit phase was acquired in the derivation cohort, whereas LAGLS only at the reservoir phase was recorded in the validation cohort. Each LAGLS was obtained from both apical four- and two-chamber views using the R-R gating method and averaged for the final analysis in both derivation and validation cohorts. EAT was identified as the echo-free space between the epicardium and right ventricular (RV) myocardium on two-dimensional echocardiography (*Figure 1*).[13] This was measured at

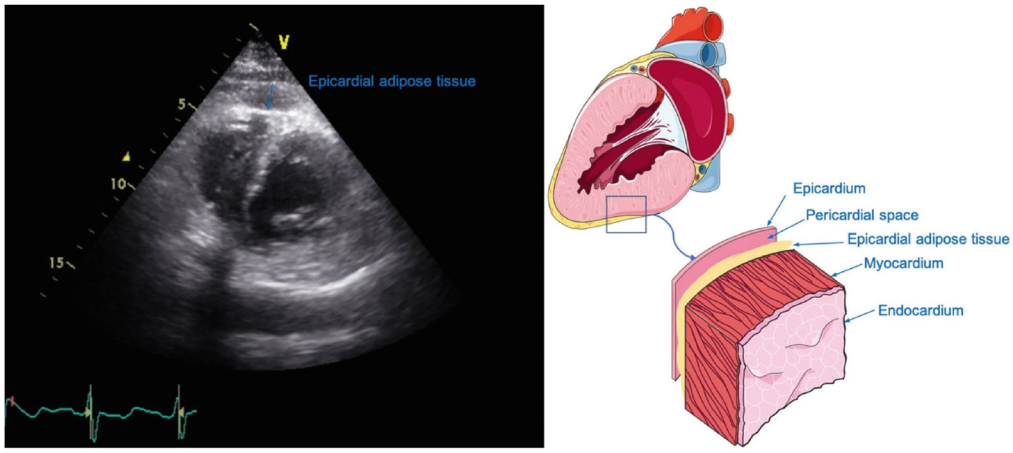

Figure 1 Anatomy of epicardial adipose tissue and example with landmark taken form the parasternal short-axis view.

end-systole in both long- and short-axis views perpendicular to the RV free wall/outflow tract, and three measurements averaged for analysis.

Statistical analysis

Data were presented as mean ± standard deviation, median (25th, 75th percentile), or number (%) for continuous with a normal distribution, continuous but skewed and categorical variables, respectively. Correspondingly, inter-group differences were tested using one-way analysis of variance (ANOVA), Kruskal–Wallis test or Mann–Whitney U test and the chi-square test, as appropriate for data type. Univariable and multivariable linear regression was used to test the association of EAT with LA, LV functional parameters, adjusted for age, sex, body mass index (BMI), atrial fibrillation (AF), CAD, hypertension, diabetes, control or HF phenotypes, LAVi, and LVEDV. Standardized beta coefficients and corresponding *p*-values were presented. Furthermore, we tested for interaction by different HF phenotypes (HFpEF vs. HFrEF/HFmrEF) on the association of EAT thickness with LA/LV function in both derivation and validation cohorts. In both derivation and validation cohorts, logistic regression was used to assess the association between thickened EAT with LA/LV dysfunction, as well as the association between LA dysfunction and HF symptomatic status based on the NYHA functional class (NYHA class ≥II vs. <II). The current study defined thickened EAT as EAT >10 mm, LV dysfunction as LVGLS <16%, and LA dysfunction as LAGLS at reservoir phase <23%. Clinically relevant subgroup analysis (AF vs. sinus rhythm, LVEF <35% vs. >65%, BMI >40 vs. <20 kg/m^2, age >80 vs. <40 years) of the EAT thickness was performed in both derivation and validation cohorts. Lastly, sensitivity analysis was performed for patients with HFmrEF (LVEF 41%–49%) in both derivation and validation cohorts. All statistical analyses were performed using SPSS (version 26, SPSS Inc, Chicago, IL, USA) and RStudio version 1.2.5033. A *p*-value <0.05 was considered statistically significant.

Results

Clinical characteristics

Clinical characteristics of patients with HFrEF/HFmrEF and HFpEF, as well as controls of both derivation and validation cohorts are summarized in *Tables 1* and *2*, respectively.

In the derivation cohort, patients with HFpEF were more likely to be older (64.6 ± 11.0 years) than patients with HFrEF/HFmrEF (57.4 ± 11.3 years) and controls (58.3 ± 10.8 years). Patients with HFpEF were more often women (37.4%) than patients with HFrEF/HFmrEF (16.4%), while controls (53.7%) were more often women as compared to patients with HFpEF and HFrEF/HFmrEF. Patients with HFpEF had higher BMI (29.2 ± 6.3 vs. 27.0 ± 5.6 kg/m^2) and were more likely to have hypertension (84.9% vs. 62.4%), diabetes (66.7% vs. 52.3%), AF (31.2% vs. 16.6%), and less likely to have CAD (47.4% vs. 63.9%), as compared to patients with HFrEF/HFmrEF (all $p < 0.05$). Prevalence of NYHA functional class ≥II in patients with HFpEF (64.9%) versus HFrEF/HFmrEF (55.4%) was not statistically different ($p = 0.093$). Patients with HFrEF/HFmrEF had higher levels of biomarkers, including NT-proBNP (median 987.5 vs. 557.5 pg/ml), growth differentiation factor-15 (GDF15, 2015.4 vs. 1775.2 pg/ml), and high-sensitivity troponin T (hsTnT, 21.7 vs. 16.7 pg/ml) than patients with HFpEF. Patients with HFpEF or HFrEF/HFmrEF had higher levels of biomarkers, including NT-proBNP, GDF15, hsTnT, ST2, and galectin-3 than controls (*Table 1*). Moreover, patients with HFrEF/HFmrEF were more likely to have a medication history with angiotensin-converting enzyme inhibitor/angiotensin receptor blocker (ACEi/ARB) (31.1% vs. 27.3%), diuretics (80.5% vs. 62.6%), and beta-blocker (65.9% vs. 53.3%), compared to patients with HFpEF. Patients with both HFpEF or HFrEF/HFmrEF had more history of medications, including ACEi/ARB, beta-blocker and statins, than controls (*Table 1*).

Similar differences were observed in the validation cohort (*Table 2*).

Echocardiographic characteristics

Echocardiographic measurements in patients with HFrEF/HFmrEF and HFpEF, and controls in the derivation and validation cohort are presented in *Tables 1* and *2*, respectively.

In the derivation cohort, patients with HFrEF/HFmrEF had larger LVEDV (136.6 ± 52.2 ml) and LVESV (93.7 ± 42.2 ml), lower

Table 1 Demographic, laboratory and echocardiographic characteristics of the derivation cohort

	Control ($n = 149$)	HFpEF ($n = 99$)	HFrEF/HFmrEF ($n = 366$)	p-value
Age (years)	58.3 ± 10.8	64.6 ± 11.0[a]	57.4 ± 11.3[c]	< 0.01
Female sex	80 (53.7)	32 (37.4)[a]	61 (16.4)[b,c]	< 0.01
Systolic BP (mmHg)	131.0 ± 16.5	137.4 ± 21.5[a]	125.2 ± 21.0[b,c]	< 0.01
Diastolic BP (mmHg)	76.1 ± 10.2	73.0 ± 13.1[a]	72.2 ± 13.8[b]	< 0.01
Heart rate (bpm)	70.4 ± 10.9	73.5 ± 11.4[a]	75.2 ± 13.7[b]	< 0.01
Body weight (kg)	65.7 ± 12.7	75.1 ± 16.7[a]	74.1 ± 17.8[b]	< 0.01
BMI (kg/m^2)	25.0 ± 3.9	29.2 ± 6.3[a]	27.0 ± 5.6[b,c]	< 0.01
Hypertension	39 (26.7)	79 (84.9)[a]	222 (62.4)[b,c]	< 0.01
AF	1 (0.7)	29 (31.2)[a]	59 (16.6)[b,c]	< 0.001
Diabetes	12 (8.1)	62 (66.7)[a]	185 (52.3)[b,c]	< 0.01
Stroke	2 (1.3)	14 (14.9)[a]	29 (8.1)[b,c]	<0.01
COPD	3 (2.0)	7 (7.4)[a]	31 (8.7)[b,c]	<0.01
NYHA class ≥II	NA	63 (64.9)	199 (55.4)	0.093
NYHA class <II	NA	34 (35.1)	160 (44.6)	
ACEi/ARB	6 (4.02)	27 (27.3)[a]	115 (31.1)[b,c]	<0.01
Diuretics	NA	62 (62.6)	298 (80.5)[b,c]	<0.01
Beta-blocker	11 (7.4)	53 (53.3)[a]	244 (65.9)[b,c]	<0.01
CCB	18 (12.1)	37 (37.4)[a]	36 (9.7)[b,c]	<0.01
Statin	36 (24.2)	72 (72.7)[a]	271 (73.2)[b]	<0.01
eGFR (ml/min/1.73 m^2)	98.3 ± 24.7	66.7 ± 27.0[a]	68.9 ± 23.6[b]	<0.01
Haematocrit (%)	41.0 ± 4.2	41.3 ± 5.6	39.6 ± 6.4[c]	0.10
NT-proBNP (pg/ml)	37.6 [21.2, 70.4]	557.5 [147.2, 1427.0][a]	978.5 [375.4, 2483.0][b,c]	<0.01
GDF15 (pg/ml)	546.3 [430.6, 792.1]	1775.2 [1016.3, 3364.7][a]	2015.4 [1207.0, 3365.5][b,c]	<0.01
hsTnT (pg/ml)	4.8 [3.2, 8.3]	16.7 [9.6, 30.3][a]	21.7 [12.3, 35.3][b,c]	<0.01
ST2 (ng/ml)	25.9 [20.4, 31.2]	29.8 [22.7, 40.3][a]	28.3 [22.6, 39.0][b]	<0.01
Galectin-3 (ng/ml)	6.5 [5.1, 8.2]	9.2 [7.2, 11.3][a]	8.9 [7.0, 10.9][b]	<0.01
LVEDV (ml)	89.0 ± 24.8	82.5 ± 31.5	136.6 ± 52.2[b,c]	< 0.01
LVESV (ml)	32.3 ± 14.6	34.3 ± 14.9	93.7 ± 42.2[b,c]	< 0.01
LVEF (%)	64.2 ± 5.8	60.4 ± 7.7[a]	33.1 ± 13.0[b,c]	< 0.01
E velocity (m/s)	0.68 ± 0.15	0.79 ± 0.29[a]	0.76 ± 0.27[b]	< 0.01
A velocity (m/s)	0.58 ± 0.16	0.78 ± 0.23[a]	0.60 ± 0.32[c]	< 0.01
E/A ratio	1.2 ± 0.5	1.0 ± 0.7	1.7 ± 1.5[b,c]	< 0.01
e′ lateral velocity (cm/s)	9.9 ± 2.7	7.5 ± 3.8[a]	6.4 ± 3.0[b,c]	< 0.01
E/e′ ratio	4.2 ± 1.1	15.8 ± 8.5[a]	13.4 ± 5.6[b]	< 0.001
LAGLS (reservoir) (%)	46.3 ± 7.3	20.7 ± 9.5[a]	17.7 ± 9.5[b,c]	< 0.01
LA dysfunction	0 (0)	46 (59.7)[a]	211 (70.8)[b,c]	< 0.001
LAGLS (contractile) (%)	20.9 ± 5.1	9.3 ± 7.7[a]	8.5 ± 6.4[b,c]	< 0.01
LAGLS (conduit) (%)	25.4 ± 6.5	11.6 ± 6.6[a]	9.3 ± 5.3[b,c]	< 0.01
LVGLS (%)	21.2 ± 3.0	14.1 ± 4.4[a]	9.6 ± 3.7[b,c]	< 0.01
LV dysfunction	5 (5.2)	51 (65.4)[a]	284 (95.0)[b,c]	< 0.01
EAT (mm)	7.9 ± 1.8	8.3 ± 2.6	7.3 ± 2.5[b,c]	< 0.01

Values are given as mean ± standard deviation, *n* (%), or median [25th, 75th percentile].

ACEi, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; BMI, body mass index; BP, blood pressure; CCB, calcium channel blocker; COPD, chronic obstructive pulmonary disease; E/A, the ratio of mitral valve early to late diastolic velocity; EAT, epicardial adipose tissue; E/e′, the ratio of mitral valve early diastolic velocity over mean value of lateral and septal mitral annular early diastolic velocity; eGFR, estimated glomerular filtration rate; GDF15, growth differentiation factor-15; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; hsTnT, high-sensitivity troponin T; LA, left atrial; LAGLS, left atrial global longitudinal strain; LV, left ventricular; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; LVGLS, left ventricular global longitudinal strain; NA, not available; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association.

[a] $p < 0.05$ for comparison of HFpEF versus controls.

[b] $p < 0.05$ for comparison of HFrEF/HFmrEF versus controls.

[c] $p < 0.05$ for comparison of HFrEF/HFmrEF versus HFpEF.

Table 2 Demographic, laboratory and echocardiographic characteristics of the validation cohort

	Control ($n = 626$)	HFpEF ($n = 243$)	HFrEF/HFmrEF ($n = 180$)	*p*-value
Age (years)	63.1 ± 12.2	71.1 ± 10.5[a]	65.9 ± 15.2[b,c]	< 0.01
Female sex	301 (48.1)	152 (62.6)[a]	60 (33.3)[b,c]	< 0.01
Systolic BP (mmHg)	139.1 ± 20.7	137.1 ± 21.1	147.1 ± 26.8[b,c]	< 0.01
Diastolic BP (mmHg)	79.1 ± 12.6	74.5 ± 11.8	83.8 ± 17.3[b,c]	< 0.01
Heart rate (bpm)	71.9 ± 14.2	73.1 ± 16.1[a]	84.5 ± 18.3[b,c]	< 0.01
BMI (kg/m^2)	26.6 ± 4.4	26.4 ± 4.1	25.3 ± 4.8[b,c]	< 0.01
Diabetes	566 (90.4)	137 (56.4)[a]	63 (35.0)[b,c]	< 0.01
Hypertension	525 (83.9)	171 (70.4)[a]	70 (38.9)[b,c]	< 0.01
AF	NA	64 (26.3)	34 (18.9)	0.073
CAD	106 (16.9)	119 (49.0)[a]	112 (62.2)[b,c]	< 0.01
Stroke	18 (2.9)	22 (9.1)	14 (7.8)	< 0.01
NYHA class ≥II	NA	134 (55.1)	103 (57.2)	0.67
NYHA class <II	NA	109 (44.9)	77 (42.8)	
ACEi/ARB	372 (59.4)	152 (62.6)	156 (86.7)[b,c]	<0.01
Diuretics	131 (20.9)	97 (39.9)[a]	148 (82.2)[b,c]	<0.01
Beta-blocker	340 (54.3)	157 (64.6)[a]	145 (80.6)[b,c]	<0.01
CCB	353 (56.4)	108 (44.4)[a]	13 (7.2)[b,c]	<0.01
Statin	221 (35.3)	102 (42.0)[a]	98 (54.4)[b,c]	<0.01
Triglyceride (mg/dl)	133 [92, 184]	116 [78, 168][a]	126 [88, 197][c]	0.013
Cholesterol (mg/dl)	188 [161, 217]	180 [154, 206]	197 [161, 236][b,c]	<0.01
LDL-cholesterol (mg/dl)	110 [88, 137]	103 [82, 125][a]	106 [82, 134][b]	0.036
HDL-cholesterol (mg/dl)	43 [36, 51]	43 [37, 54]	39 [32, 48][b,c]	<0.01
Fasting blood glucose (mg/dl)	128 [111, 153]	110 [101, 141]	138 [101, 185][b,c]	<0.01
hsCRP (mg/dl)	0.18 [0.09, 0.40]	0.21 [0.09, 0.49]	0.21 [0.06, 0.56]	0.56
eGFR (ml/min/1.73 m^2)	78.3 ± 28.9	58.6 ± 28.5[a]	49.5 ± 28.6[b,c]	< 0.01
BNP	NA	89 [31, 275]	605 [188, 1480][c]	< 0.01
LVEDD (mm)	46.6 ± 4.5	46.7 ± 4.8	54.2 ± 9.3[b,c]	< 0.01
LVESD (mm)	30.1 ± 3.6	30.7 ± 4.3	43.1 ± 11.9[b,c]	< 0.01
IVS (mm)	10.1 ± 1.6	10.1 ± 1.7	9.7 ± 2.0[c]	0.01
LVPW (mm)	10.1 ± 1.6	10.3 ± 1.7	9.8 ± 1.9[c]	0.016
LVMi (g/m^2)	89 ± 22	94 ± 27[a]	110 ± 35[b,c]	<0.01
LVEF (%)	64.3 ± 6.5	62.9 ± 6.8	39.5 ± 20.0[b,c]	<0.01
E/A ratio	1.0 ± 0.5	1.0 ± 0.8	1.5 ± 1.2[b,c]	<0.01
LAVi (ml/m^2)	19.4 ± 7.8	26.2 ± 13.7[a]	32.8 ± 15.8[b,c]	<0.01
LAGLS (reservoir) (%)	27.3 ± 7.7	23.1 ± 7.1[a]	20.8 ± 3.4[b,c]	< 0.01
LA dysfunction	137 (27.7)	106 (47.3)[a]	129 (72.1)[b,c]	< 0.01
LVGLS (%)	18.5 ± 2.9	17.1 ± 3.6[a]	15.2 ± 2.0[b,c]	< 0.01
LV dysfunction	109 (18.0)	83 (34.7)[a]	99 (55.0)[b,c]	< 0.01
EAT (mm)	7.7 ± 2.3	9.6 ± 2.8[a]	6.7 ± 1.4[b,c]	< 0.01

Values are given as mean ± standard deviation, *n* (%), or median [25th, 75th percentile].
ACEi, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; BP, blood pressure; BMI, body mass index; BNP, B-type natriuretic peptide; CAD, coronary artery disease; CCB, calcium channel blocker; E/A, the ratio of mitral valve early to late diastolic velocity; EAT, epicardial adipose tissue; eGFR, estimated glomerular filtration rate; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HDL, high-density lipoprotein; hsCRP, high-sensitivity C-reactive protein; IVS, interventricular septal wall thickness; LA, left atrial; LAGLS, left atrial global longitudinal strain; LAVi, left atrial volume index; LDL, low-density lipoprotein; LV, left ventricular; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; LVGLS, left ventricular global longitudinal strain; LVMi, left ventricular mass index; LVPW, left ventricular posterior wall thickness; NA, not available; NYHA, New York Heart Association.
[a] $p < 0.05$ for comparison of HFpEF versus controls.
[b] $p < 0.05$ for comparison of HFrEF/HFmrEF versus controls.
[c] $p < 0.05$ for comparison of HFrEF/HFmrEF versus HFpEF.

Table 3 Association of epicardial adipose tissue with left atrial/left ventricular function in the derivation and validation cohorts

	Derivation cohort			Validation cohort		
	Standardized β coefficient	*p*-value	$p_{interaction}$ (LA/LV GLS x HF group [HFpEF vs. HFrEF/HFmrEF])	Standardized β coefficient	*p*-value	$p_{interaction}$ (LA/LV GLS x HF group [HFpEF vs. HFrEF/HFmrEF])
LAGLS (contractile)				LAGLS (reservoir)		
Univariate	0.14	0.008	<0.01	−0.23	<0.001	<0.01
Model A	0.17	<0.001	–	−0.19	<0.001	–
Model B	0.18	0.003	–	−0.19	<0.001	–
Model C	0.16	0.006	–	−0.19	<0.001	–
LVGLS						
Univariate	0.12	0.022	0.01	−0.11	<0.001	<0.01
Model A	0.06	0.064	–	−0.18	<0.001	–
Model B	0.09	0.075	–	−0.17	<0.001	–
Model C	0.07	0.142	–	−0.18	<0.001	–

AF, atrial fibrillation; BMI, body mass index; CAD, coronary artery disease; HF, heart failure; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LAGLS, left atrial global longitudinal strain; LAVi, left atrial volume index; LVEDV, left ventricular end-diastolic volume; LVGLS, left ventricular global longitudinal strain.
Model A: adjusted for age, sex, AF, BMI, hypertension, diabetes, CAD, and HF group.
Model B: adjusted for variables from model A and LVEDV.
Model C: adjusted for variables from model B and LAVi.

absolute values of LVGLS (9.6 ± 3.7%) and worse LV diastolic function (lower e′ velocity and E/A ratio), compared to both patients with HFpEF and controls. Compared to controls, patients with HFpEF had similar LV sizes (LVEDV, 82.5 ± 31.5 vs. 89.0 ± 24.8 ml, $p > 0.05$), but significantly worse LV systolic (LVGLS, 14.1 ± 4.4% vs. 21.2 ± 3.0%), diastolic (e′ velocity, 7.5 ± 3.8 vs. 9.9 ± 2.7 cm/s), and LA function evaluated by LAGLS assessments at all phases, including reservoir (20.7 ± 9.5% vs. 46.3 ± 7.3%), contractile (9.3 ± 7.7% vs. 20.9 ± 5.1%), and conduit (11.6 ± 6.6% vs. 25.4 ± 6.5%) phase (all $p < 0.05$). LA dysfunction was most prominent in patients with HFrEF/HFmrEF (70.8%) among groups, and patients with HFpEF (59.7%) had more LA dysfunction than controls ($p < 0.01$).

Echocardiographic characteristics of the validation cohort resembled those of the derivation cohort (*Table 2*).

Association between epicardial adipose tissue and left atrial/left ventricular function in the derivation cohort

In the derivation cohort, patients with HFrEF/HFmrEF had lower EAT thickness (7.3 ± 2.5 mm) than patients with HFpEF (8.3 ± 2.6 mm, $p < 0.05$) and controls (7.9 ± 1.8 mm, $p < 0.05$). Although mean EAT thickness was greater in HFpEF compared to controls, this difference did not reach statistical significance. In the entire derivation cohort, greater EAT thickness was associated with better LA function (LAGLS at contractile phase, standardized β coefficient 0.16, $p = 0.006$, and LAGLS at reservoir phase, standardized β coefficient 0.11, $p = 0.017$), independent of age, sex, AF, BMI, hypertension, diabetes, CAD, control/HF group, LVEDV and LAVi. EAT thickness was not associated with LAGLS at conduit phase (standardized β coefficient 0.04, $p = 0.50$), and the association of EAT thickness with LAGLS at reservoir phase in HFpEF versus HFrEF/HFmrEF was marginally different (p for interaction = 0.08). Greater EAT thickness was associated with better LV function (LVGLS, standardized β coefficient 0.12, $p = 0.022$), but the association was attenuated after multivariable adjustment (standardized β coefficient 0.07, $p = 0.14$) (*Table 3*). These associations differed by HF phenotype – greater EAT thickness was associated with better contractile LA function (LAGLS at contractile phase, standardized β coefficient 0.15, $p = 0.02$) and LV function (LVGLS, standardized β coefficient 0.13, $p = 0.03$) in HFrEF/HFmrEF, but not HFpEF (LAGLS at contractile phase, standardized β coefficient −0.21, $p = 0.13$; LVGLS, standardized β coefficient −0.19, $p = 0.17$; *Figure 2*). The association of EAT with better contractile LA and LV function in patients with HFrEF/HFmrEF remained significant after adjusting for age, sex, AF, BMI, hypertension, diabetes, CAD, and LA/LV size. The associations of thickened EAT (EAT >10 mm) with LA and LV dysfunction are provided in online supplementary Table *S1*. Although the point estimates showed increased odds of LV and LA dysfunction with thickened EAT in HFpEF, in contrast to reduced odds in HFrEF/HFmrEF, these associations were not statistically significant. LA dysfunction was associated with worse symptomatic status (based on NYHA functional class ≥II) in both HFpEF (odds ratio [OR] 3.63, 95% confidence interval [CI] 1.34–9.83, $p < 0.01$) and HFrEF/HFmrEF (OR 3.03, 95% CI 1.80–5.12, $p < 0.01$) in the derivation cohort.

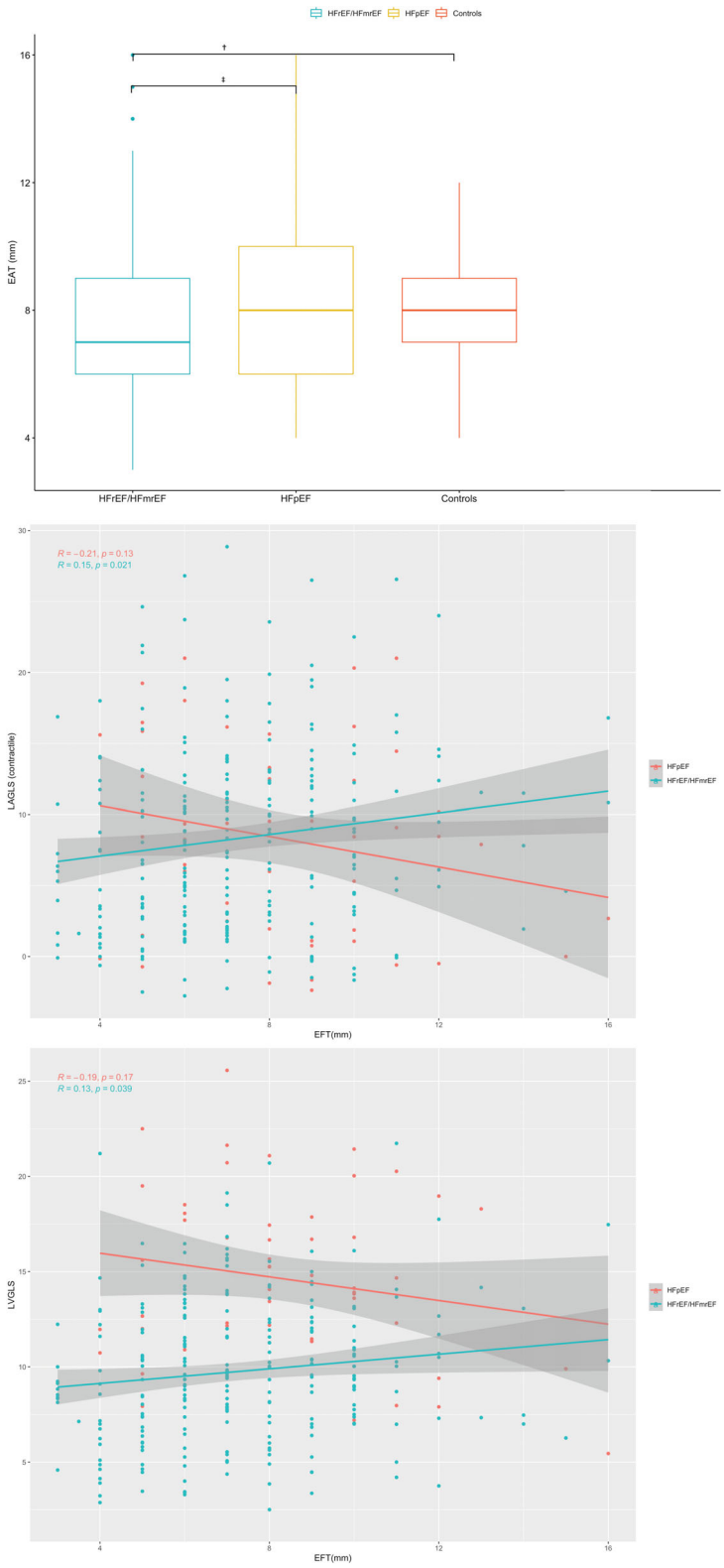

Figure 2 Bar charts comparing epicardial adipose tissue (EAT) in patients with heart failure with preserved (HFpEF) versus reduced/mildly reduced ejection fraction (HFrEF/HFmrEF) versus control patients, and differential association of EAT with left atrial and left ventricular function in HFpEF versus HFrEF/HFmrEF in the derivation cohort. *$p < 0.05$ for comparison of HFpEF versus controls. $^{\dagger}p < 0.05$ for comparison of HFrEF/HFmrEF versus controls. $^{\ddagger}p < 0.05$ for comparison of HFrEF/HFmrEF versus HFpEF. EFT, epicardial fat thickness; LAGLS, left atrial global longitudinal strain; LVGLS, left ventricular global longitudinal strain.

Association between epicardial adipose tissue and left atrial/left ventricular function in the validation cohort

In the validation cohort, EAT thickness was similarly lower in patients with HFrEF/HFmrEF (6.7 ± 1.4 mm) as compared to patients with HFpEF and controls. Patients with HFpEF also had significantly higher EAT thickness (9.6 ± 2.8 mm) as compared to control patients (7.7 ± 2.3 mm). Unlike the derivation cohort, greater EAT thickness was associated in the entire validation cohort with worse reservoir LA (LAGLS at reservoir phase, standardized β coefficient − 0.19, $p < 0.001$) and LV function (LVGLS, standardized β coefficient − 0.18, $p < 0.001$), independent of age, sex, AF, BMI, hypertension, diabetes, CAD, control/HF group, LVEDV and LAVi. The differential association between EAT thickness and reservoir LA/LV function in patients with HFpEF versus HFrEF/HFmrEF was confirmed (*Figure 3*). Greater EAT thickness was associated with worse reservoir LA (LAGLS at reservoir phase, standardized β coefficient − 0.29, $p < 0.01$) and LV (standardized β coefficient − 0.17, $p < 0.01$) function in HFpEF, but better reservoir LA (LAGLS at reservoir phase, standardized β coefficient 0.14, $p = 0.066$) and LV (standardized β coefficient 0.27, $p < 0.01$) function in HFrEF/HFmrEF. The association of EAT with LVGLS remained significant even after adjusting for age, sex, AF, BMI, hypertension, diabetes, CAD, and LVEDV in patients with HFrEF/HFmrEF and HFpEF. However, the associations of EAT with LAGLS at reservoir phase were attenuated after adjustment. Thickened EAT (>10 mm) was associated with LA dysfunction (LAGLS at reservoir phase <23%, OR 2.15, 95% CI 1.26–3.66, $p = 0.005$) in patients with HFpEF, but not in patients with HFrEF/HFmrEF despite a higher prevalence of LA dysfunction in HFrEF/HFmrEF (72.1%) than HFpEF (47.3%, $p < 0.01$). Moreover, LA dysfunction was associated with worse NYHA class function (OR 5.10, 95% CI 2.87–9.08, $p < 0.01$) in HFpEF, but not in HFrEF/HFmrEF (OR 1.71, 95% CI 0.89–3.31, $p = 0.13$). Turning to the left ventricle, thickened EAT was marginally associated with LV dysfunction (LVGLS <16%, OR 1.68, 95% CI 0.98–2.98, $p = 0.06$) in HFpEF, but not in HFrEF/HFmrEF (online supplementary *Tables S1–S3*). Results of the subgroup analysis are presented in the online supplementary material.

Sensitivity analysis in the derivation and validation cohorts

In sensitivity analysis, patients with HFmrEF (LVEF 41%–49%, $n = 64$) had similar clinical characteristics as compared to patients with HFrEF (LVEF <40%) in the derivation cohort, including BMI (27.5 ± 5.2 vs. 26.8 ± 5.6 kg/m^2, $p = 0.41$), AF (18.7% vs. 16.1%, $p = 0.36$), CAD (61.9% vs. 64.3%, $p = 0.40$), hypertension (70.3% vs. 60.6%, $p = 0.09$), diabetes (50.0% vs. 52.7%, $p = 0.40$), and EAT thickness (7.9 ± 2.3 vs. 7.2 ± 2.5 mm, $p = 0.09$). Similar findings of clinical characteristics and EAT thickness (6.7 ± 1.2 vs. 6.7 ± 1.4 mm, $p = 0.87$) between patients with HFmrEF (LVEF 41%–49%, $n = 25$) and patients with HFrEF (LVEF <40%) were observed in the validation cohort. After excluding those with HFmrEF, findings regarding EAT in both derivation and validation cohorts remained consistent.

Discussion

From the present study comparing EAT thickness and its association with LA and LV function in patients with HFpEF, HFrEF/HFmrEF, and control subjects we can draw main conclusions as follows. First, EAT thickness was greatest in patients with HFpEF and lowest in patients with HFrEF/HFmrEF. Second, greater thickness of EAT was associated with worse reservoir or contractile LA and LV function in patients with HFpEF but better reservoir or contractile LA and LV function in HFrEF/HFmrEF. Despite a higher prevalence of LA dysfunction in HFrEF/HFmrEF than HFpEF, thickened EAT was associated with LA dysfunction in HFpEF but not HFrEF/HFmrEF, suggesting a potential mechanistic link between EAT thickening and LA dysfunction in HFpEF.

Several studies compared EAT thickness and mass between patients with HFpEF and control subjects. Van Woerden *et al.*[14] found that EAT mass, assessed by magnetic resonance imaging (MRI), was greater in patients with HFpEF than control subjects. Similarly, Obokata *et al.*[15] showed that EAT thickness, assessed by echocardiography, was greater in patients with HFpEF compared to control subjects. In contrast, Haykowsky *et al.*[6] showed that EAT mass, measured by MRI, was lower in obese HFpEF patients than control subjects. Studies comparing EAT thickness and mass in patients with HFrEF/HFmrEF versus control subjects also showed inconsistent results. Doesch *et al.*[10] showed lower EAT mass in patients with HFrEF than control patients, and Iacobellis *et al.*[16] found lower EAT thickness in patients with HFrEF/HFmrEF and AF as compared to patients with AF alone without HF. Only few studies compared EAT between patients with HFpEF, HFrEF, and controls. Wu *et al.*[17] found that patients with HFrEF had lower intramyocardial fat than patients with HFpEF and control patients despite greater EAT mass by MRI in patients with HFrEF (41 g) versus HFpEF (31 g) and control patients (26 g). The most recent study by Pugliese *et al.*[18] found that patients with HFrEF/HFmrEF had the lowest EAT (3 mm) by echocardiography and patients with HFpEF had highest EAT (8 mm) than controls (5 mm). Thus, our findings were consistent with most, but not all studies, in showing that EAT thickness is greatest in HFpEF and lowest in HFrEF/HFmrEF.

Potential explanations behind our observation of greater EAT thickness in HFpEF than in HFrEF/HFmrEF can be twofold. First, patients with HFpEF generally have a higher BMI compared to those with HFrEF/HFmrEF,[16,19] suggesting greater overall adiposity which may also be reflected by greater excess epicardial fat deposition. A second explanation for our finding that EAT thickness was lower in HFrEF/HFmrEF than HFpEF might be that HFrEF/HFmrEF hearts are more dilated and the same amount of fat is distributed over a larger surface, leading to lower thickness.[10,20–22]

The most important and novel finding of the present study was that there was a differential association between EAT thickness and LA/LV function in patients with HFrEF/HFmrEF and HFpEF. The initial discrepant association of EAT thickness with LA/LV

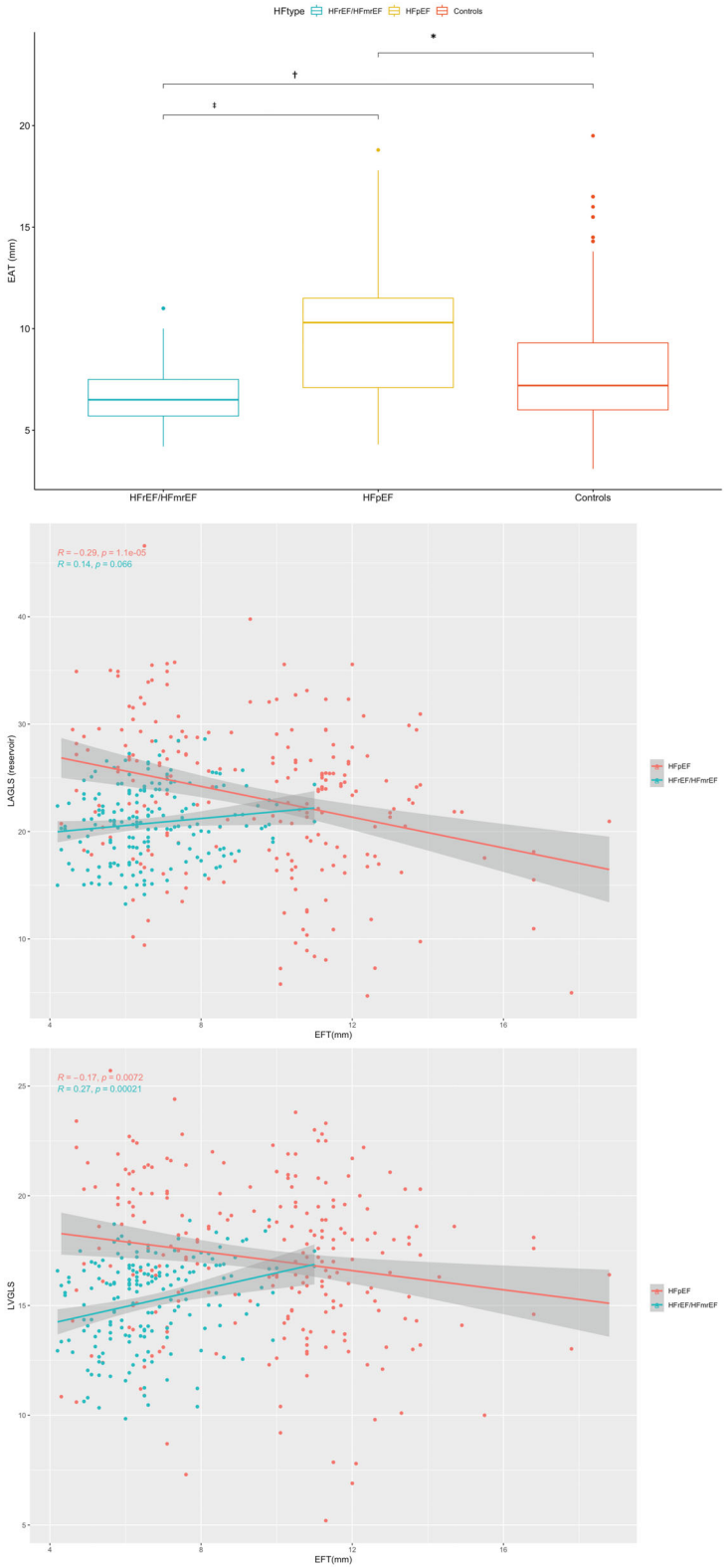

Figure 3 Bar charts comparing epicardial adipose tissue (EAT) in patients with heart failure with preserved (HFpEF) versus reduced/mildly reduced ejection fraction (HFrEF/HFmrEF) versus control patients, and differential association of EAT with left atrial and left ventricular function in HFpEF versus HFrEF/HFmrEF in the validation cohort. $^{*}p < 0.05$ for comparison of HFpEF versus controls. $^{\dagger}p < 0.05$ for comparison of HFrEF/HFmrEF versus controls. $^{\ddagger}p < 0.05$ for comparison of HFrEF/HFmrEF versus HFpEF. EFT, epicardial fat thickness; LAGLS, left atrial global longitudinal strain; LVGLS, left ventricular global longitudinal strain.

function in the derivation versus validation cohorts might be explained by the different proportions of patients with HFpEF versus HFrEF/HFmrEF, with HFrEF/HFmrEF patients constituting a larger proportion of the entire derivation cohort, and HFpEF patients comprising a larger proportion of the entire validation cohort. The relationship between EAT thickness and contractile or reservoir LA/LV function in both derivation and validation cohorts were influenced by HF type, independent of age, sex, BMI, LA and LV size (p for interaction <0.05 for both derivation and validation cohorts) – greater EAT thickness was associated with better contractile or reservoir LA and LV function in HFrEF/HFmrEF, but not in HFpEF. Besides, LA dysfunction was associated with thickened EAT in HFpEF, but not in HFrEF/HFmrEF. Doesch *et al.*[10] found that lower EAT mass was associated with worse LV systolic function in patients with HFrEF, which is in line with our findings. Two other studies showed that increased amounts of EAT in patients with HFpEF were associated with higher right-sided filling pressures and pulmonary hypertension.[7,8]

A potential explanation for this differential association between EAT and cardiac function in HFpEF versus HFrEF/HFmrEF might be related to a different fat quality or composition in patients with HFpEF versus HFrEF/HFmrEF. For instance, a predominance of white fat in EAT among patients with HFpEF may exert cardiodepressive effects; whereas brown fat in EAT among patients with HFrEF/HFmrEF may be metabolically efficient and help improve cardiac function and contractility.[2,5,24] Studies have suggested that brown fat-like EAT is actively engaged in lipid and energy homeostasis and serves as a source of energy via the transmit of free fatty acids, and the oxidation of free fatty acids accounts for up to 70% of cardiac energy production.[5,13,24] Indeed, an experimental study found remarkably reduced brown fat-related gene expression of EAT in HFrEF/HfmrEF as compared to controls, which further supports this hypothesis.[5,9] Alternatively, we postulate that excess fat accumulation in EAT in HFpEF may be prone to inflammation, promoting microvascular inflammation and fibrosis via the release of inflammatory cytokines to the adjacent myocardium (e.g. adiponectin) resulting in atrial and ventricular dysfunction.[2,24,25] Indeed, prior studies have demonstrated the presence of coronary microvascular dysfunction and myocardial inflammation in HFpEF,[24–28] and EAT has been associated with myocardial fibrosis in HFpEF, but not in HFrEF/HFmrEF.[11] Collectively, the different composition and quality of EAT between HFrEF/HFmrEF and HFpEF might explain the differential association between EAT thickness and LA/LV function.

Limitations

A direct causal relationship between EAT and cardiac function cannot be concluded from these observational cross-sectional results. We did not have sufficient information on biomarkers of inflammation to perform mediation analyses. We defined HFrEF as a LVEF <50%, and therefore included patients with HFmrEF. However, increasing data suggest that in terms of aetiology and response to therapies, HFmrEF is more like HFrEF than HFpEF,[29] and sensitivity analyses excluding patients with HFmrEF in the current study gave similar results. Different association of EAT with LAGLS at contractile versus reservoir phase in the derivation versus validation should be mentioned. Of note, despite differences between LAGLS at reservoir versus contractile phase, all the trends regarding LAGLS among different groups and its association with EAT in HFpEF versus HFrEF/HFmrEF were similar between derivation and validation cohorts. The current study only assessed the quantity and not the quality of EAT, and measured EAT only over the RV free wall – a limitation intrinsic to echocardiography as an imaging tool to assess EAT. However, ~75% of total EAT is estimated to be located over the right ventricle, and in our prior study using both MRI (for total EAT mass) and echocardiography (EAT thickness) to assess EAT in each patient, there was consistency in the group patterns (HFpEF vs. HFrEF/HFmrEF vs. controls) by both techniques.[11]

Conclusions

In two independent cohorts, EAT thickness was greater in patients with HFpEF than HFrEF/HFmrEF. We found opposing relationships between EAT thickness and left-sided cardiac function in patients with HFpEF versus HFrEF/HFmrEF, whereby greater EAT thickness was associated with worse contractile or reservoir LA/LV function in HFpEF, but better contractile or reservoir LA/LV function in HFrEF/HFmrEF.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Conflict of interest: C.S.P.L. is supported by a Clinician Scientist Award from the National Medical Research Council of Singapore; has received research support from AstraZeneca, Bayer, Boston Scientific and Roche Diangostics; has served as consultant or on the Advisory Board/ Steering Committee/Executive Committee for Actelion, Amgen, Applied Therapeutics, AstraZenea, Bayer, Boehringer Ingelheim, Boston Scientific, Cytokinetics, Darma Inc., Janssen Research & Development LLC, Medscape/WebMD Global LLC, Merck, Novartis, Novo Nordisk, Radcliffe Group Ltd., Roche Diagnostics, Sanofi and Us2.ai. All other authors have nothing to disclose.

References

1. Redfield MM. Heart failure with preserved ejection fraction. *N Engl J Med*. 2016;**375**:1868–77.
2. 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.
3. Chan MM, Lam CS. How do patients with heart failure with preserved ejection fraction die? *Eur J Heart Fail*. 2013;**15**:604–13.
4. Tomasoni D, Adamo M, Lombardi CM, Metra M. Highlights in heart failure. *ESC Heart Fail*. 2019;**6**:1105–27.
5. Iacobellis G, Barbaro G. Epicardial adipose tissue feeding and overfeeding the heart. *Nutrition*. 2019;**59**:1–6.
6. Haykowsky MJ, Nicklas BJ, Brubaker PH, Hundley WG, Brinkley TE, Upadhya B, et al. Regional adipose distribution and its relationship to exercise intolerance in older obese patients who have heart failure with preserved ejection fraction. *JACC Heart Fail*. 2018;**6**:640–9.

7. Koepp KE, Obokata M, Reddy YNV, Olson TP, Borlaug BA. Hemodynamic and functional impact of epicardial adipose tissue in heart failure with preserved ejection fraction. *JACC Heart Fail.* 2020;**8**:657–66.
8. Gorter TM, van Woerden G, Rienstra M, Dickinson MG, Hummel YM, Voors AA, et al. Epicardial adipose tissue and invasive hemodynamics in heart failure with preserved ejection fraction. *JACC Heart Fail*. 2020;**8**:667–76.
9. Perez-Belmonte LM, Moreno-Santos I, Gomez-Doblas JJ, Garcia-Pinilla JM, Morcillo-Hidalgo L, Garrido-Sanchez L, et al. Expression of epicardial adipose tissue thermogenic genes in patients with reduced and preserved ejection fraction heart failure. *Int J Med Sci*. 2017;**14**:891–5.
10. Doesch C, Haghi D, Fluchter S, Suselbeck T, Schoenberg SO, Michaely H, et al. Epicardial adipose tissue in patients with heart failure. *J Cardiovasc Magn Reson*. 2010;**12**:40.
11. Tromp J, Bryant JA, Jin X, van Woerden G, Asali S, Yiying H, Liew OW, et al. Epicardial fat in heart failure with reduced versus preserved ejection fraction. *Eur J Heart Fail*. 2021;**23**:835–8.
12. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr*. 2015;**28**: 1–39.e14.
13. Iacobellis G. *Epicardial adipose tissue: from cell to clinic*. Cham: Springer; 2020.
14. van Woerden G, Gorter TM, Westenbrink BD, Willems TP, van Veldhuisen DJ, Rienstra M. Epicardial fat in heart failure patients with mid-range and preserved ejection fraction. *Eur J Heart Fail*. 2018;**20**:1559–66.
15. Obokata M, Reddy YNV, Pislaru SV, 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.
16. Iacobellis G, Zaki MC, Garcia D, Willens HJ. Epicardial fat in atrial fibrillation and heart failure. *Horm Metab Res*. 2014;**46**:587–90.
17. Wu CK, Lee JK, Hsu JC, Su MM, Wu YF, Lin TT, et al. Myocardial adipose deposition and the development of heart failure with preserved ejection fraction. *Eur J Heart Fail*. 2020;**22**:445–54.
18. Pugliese NR, Paneni F, Mazzola M, De Biase N, Del Punta L, Gargani L, et al. Impact of epicardial adipose tissue on cardiovascular haemodynamics, metabolic profile, and prognosis in heart failure. *Eur J Heart Fail*. 2021;**23**: 1858–71.
19. Savji N, Meijers WC, Bartz TM, Bhambhani V, Cushman M, Nayor M, et al. The association of obesity and cardiometabolic traits with incident HFpEF and HFrEF. *JACC Heart Fail*. 2018;**6**:701–9.
20. Katz DH, Beussink L, Sauer AJ, Freed BH, Burke MA, Shah SJ. Prevalence, clinical characteristics, and outcomes associated with eccentric versus concentric left ventricular hypertrophy in heart failure with preserved ejection fraction. *Am J Cardiol*. 2013;**112**:1158–64.
21. Nauta JF, Hummel YM, Tromp J, Ouwerkerk W, van der Meer P, Jin X, et al. Concentric vs. eccentric remodelling in heart failure with reduced ejection fraction: clinical characteristics, pathophysiology and response to treatment. *Eur J Heart Fail*. 2020;**22**:1147–55.
22. Corradi D, Maestri R, Callegari S, Pastori P, Goldoni M, Luong TV, et al. The ventricular epicardial fat is related to the myocardial mass in normal, ischemic and hypertrophic hearts. *Cardiovasc Pathol*. 2004;**13**:313–6.
23. Pathan F, D'Elia N, Nolan MT, Marwick TH, Negishi K. Normal ranges of left atrial strain by speckle-tracking echocardiography: a systematic review and meta-analysis. *J Am Soc Echocardiogr*. 2017;**30**:59–70.e58.
24. Tromp J, Westenbrink BD, Ouwerkerk W, van Veldhuisen DJ, Samani NJ, Ponikowski P, et al. Identifying pathophysiological mechanisms in heart failure with reduced versus preserved ejection fraction. *J Am Coll Cardiol*. 2018;**72**:1081–90.
25. 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.
26. Westermann D, Lindner D, Kasner M, Zietsch C, Savvatis K, Escher F, et al. Cardiac inflammation contributes to changes in the extracellular matrix in patients with heart failure and normal ejection fraction. *Circ Heart Fail*. 2011;**4**:44–52.
27. Shah SJ, Lam CSP, Svedlund S, Saraste A, Hage C, Tan RS, et al. Prevalence and correlates of coronary microvascular dysfunction in heart failure with preserved ejection fraction: PROMIS-HFpEF. *Eur Heart J*. 2018;**39**:3439–50.
28. Sanders-van Wijk S, Tromp J, Beussink-Nelson L, Hage C, Svedlund S, Saraste A, et al. Proteomic evaluation of the comorbidity-inflammation paradigm in heart failure with preserved ejection fraction: results from the PROMIS-HFpEF study. *Circulation*. 2020;**142**:2029–44.
29. Koufou EE, Arfaras-Melainis A, Rawal S, Kalogeropoulos AP. Treatment of heart failure with mid-range ejection fraction: what is the evidence. *J Clin Med*. 2021;**10**:203.