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# Epicardial adipose tissue volume and density are associated with heart failure with improved ejection fraction

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## Abstract

**Background** Heart failure (HF) with improved ejection fraction (EF, HFimpEF) is a distinct HF subtype, characterized by left ventricular (LV) reverse remodeling and myocardial functional recovery. Multiple cardiometabolic factors are implicated in this process. Epicardial adipose tissue (EAT), emerging as an endocrine and paracrine organ, contributes to the onset and progression of HF. However, the relation between EAT and the incidence of HFimpEF is still unclear.

**Methods** A total of 203 hospitalized HF patients with reduced EF (HFrEF, LVEF  $\leq$  40%) who underwent coronary CT angiography (CCTA) during index hospitalization were consecutively enrolled between November 2011 and December 2022. Routine follow-up and repeat echocardiograms were performed. The incidence of HFimpEF was defined as (1) an absolute LVEF improvement  $\geq$  10% and (2) a second LVEF  $>$  40% (at least 3 months apart). EAT volume and density were semiautomatically quantified on non-enhanced series of CCTA scans.

**Results** During a median follow-up of 8.6 (4.9~13.3) months, 104 (51.2%) patients developed HFimpEF. Compared with HFrEF patients, HFimpEF patients had lower EAT volume (115.36 [IQR 87.08~154.78] mL vs. 169.67 [IQR 137.22~218.89] mL,  $P < 0.001$ ) and higher EAT density ( $-74.92 \pm 6.84$  HU vs.  $-78.76 \pm 6.28$  HU,  $P < 0.001$ ). Multivariate analysis showed lower EAT volume (OR: 0.885 [95%CI 0.822~0.947]) and higher density (OR: 1.845 [95%CI 1.023~3.437]) were both independently associated with the incidence of HFimpEF. Subgroup analysis revealed that the association between EAT properties and HFimpEF was not modified by HF etiology.

**Conclusions** This study reveals that lower EAT volume and higher EAT density are associated with development of HFimpEF. Therapies targeted at reducing EAT quantity and improving its quality might provide favorable effects on myocardial recovery in HF patients.

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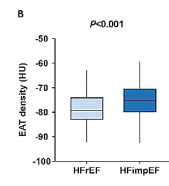
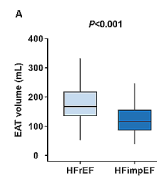
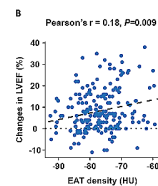
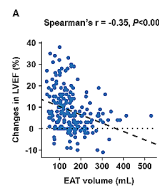
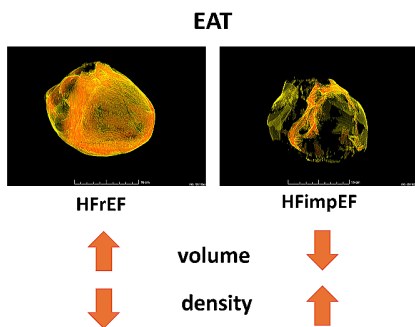
Graphical abstract

CENTRAL ILLUSTRATION Epicardial Adipose Tissue Volume and Density are Associated with Heart Failure with Improved Ejection Fraction

203 HFrEF patients who underwent CCTA (2011/11-2022/12)

8.6 (4.9~13.3) months follow-up

HFimpEF (n=104) ■ Second LVEF > 40% AND LVEF absolute increase ≥ 10%  
 HFrEF (n=99) ■ Second LVEF ≤ 40% OR LVEF absolute increase < 10%



Multivariate analysis showed **lower EAT volume** (OR: 0.885 [95%CI 0.822~0.947]) and **higher density** (OR: 1.845 [95%CI 1.023~3.437]) were both independently associated with the incidence of HFimpEF.

Lower EAT volume and higher EAT density are independently associated with development of HFimpEF.

**Keywords** Epicardial adipose tissue, Heart failure with improved ejection fraction, Heart failure with reduced ejection fraction, Myocardial recovery

Background

Attributed to the development of guideline-based medical and device therapies, a substantial portion of heart failure (HF) patients with reduced ejection fraction (EF, HFrEF) have experienced partial or complete myocardial recovery [1, 2]. According to the 2022 AHA/ACC/HFSA Guideline for the Management of HF, patients with previous HFrEF whose left ventricular EF (LVEF) develops to >40% are now termed as "HF with improved EF" (HFimpEF) [3]. Existing evidence shows that HFimpEF is a distinct HF phenotype underlined by coordinated changes in gene transcription, adaptation of cellular and metabolic processes, and alteration of extracellular matrix composition, thereby leading to improved cardiomyocyte contractility and left ventricular (LV) geometric restoration [4–6]. Development of HFimpEF is generally considered as a surrogate endpoint representing a better cardiovascular prognosis. However, the predictors for HFimpEF are still being explored.

Epicardial adipose tissue (EAT), a layer of adipose tissue located between the myocardium and visceral pericardium, has been widely recognized as an endocrine and paracrine organ [7, 8]. Due to its unobstructed proximity and shared microcirculation, EAT has a direct cross-talk with adjacent myocardium. Physiologically, EAT

serves as a heart protector by mechanical, thermogenic, metabolic, and paracrine mechanisms [9, 10]. Under certain pathological conditions, EAT tends to switch to a pro-inflammatory, immune-responsive, and pro-fibrosis state, which is also reflected by geometric and compositional changes of EAT from a macro perspective [7, 11, 12]. Current data demonstrate that EAT is closely implicated in the development of various cardiovascular diseases including coronary heart disease, atrial fibrillation and HF [13, 14]. Especially, the crucial role of EAT in HF has been verified by a number of studies, mainly focusing on HF with preserved EF (HFpEF) [15–17]. Nevertheless, the impact of EAT on LV reverse remodeling and myocardial recovery remains unknown. In the present study, we sought to investigate the association between EAT assessed by cardiac CT and the incidence of HFimpEF.

Methods

Study population

The study consecutively enrolled 402 patients who were diagnosed with HFrEF (LVEF ≤ 40%) and underwent coronary CT angiography (CCTA) during index hospitalization between November 2011 and December 2022 in Shanghai Ruijin Hospital. A total of 98 patients comorbid with pericardial diseases ( $n = 24$ ), malignant tumor

( $n=19$ ), heart transplantation ( $n=1$ ), prior cardiac surgery ( $n=51$ ), and in-hospital death ( $n=3$ ) were excluded. The enrolled patients were routinely followed up and underwent repeat echocardiograms. During follow-up, there were 15 deaths and 86 patients lost to echocardiogram follow-up, who were also excluded (Fig. 1).

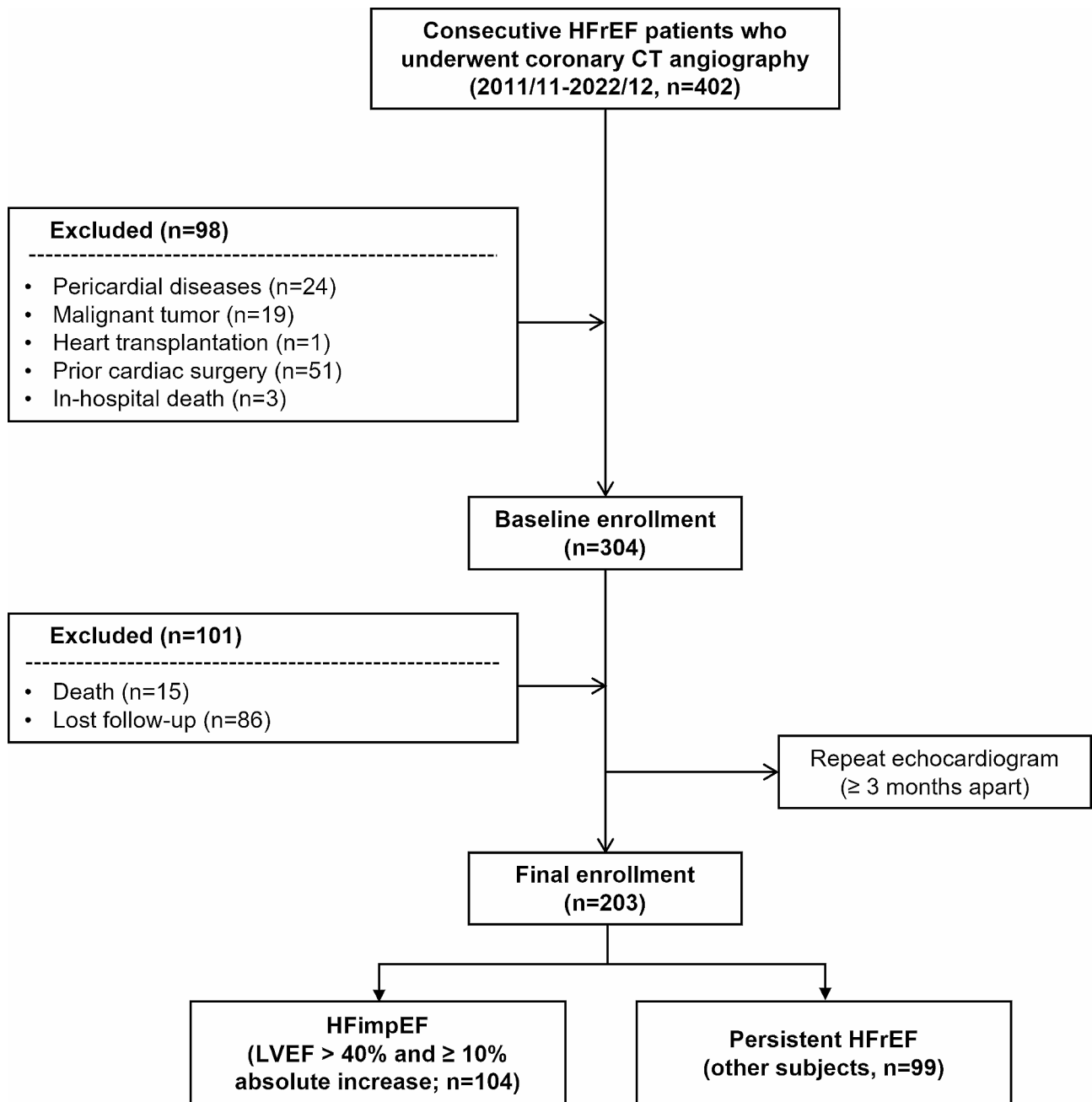
The primary outcome was the development of HFimpEF, which was diagnosed based on repeat echocardiograms  $\geq 3$  months apart according to the working

definition of HFimpEF: (1)  $\geq 10\%$  absolute LVEF improvement; and (2) a second LVEF  $> 40\%$ .

This study complies with the Declaration of Helsinki. The study protocol was approved by Shanghai Ruijin Hospital ethics committee, and written informed consent was obtained from all participants.

**Clinical and biochemical assessments**

Detailed information of medical history and lifestyles including smoking habits was obtained using a



**Fig. 1** Flowchart of patient enrollment. HFimpEF heart failure with improved ejection fraction, HFREF heart failure with reduced ejection fraction, LVEF left ventricular ejection fraction

standard questionnaire by trained physicians on admission. Body mass index (BMI) was calculated as weight/height<sup>2</sup> (kilograms per square meter). Body surface area (BSA) was calculated by Stevenson's formula:  $0.0061 \times \text{height} + 0.0128 \times \text{weight} - 0.1529$ . Hypertension was diagnosed according to the seventh report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure (BP; JNC 7). The diagnosis of diabetes was made according to the criteria of American Diabetes Association.

All the blood samples were drawn after overnight fasting. Plasma glucose, liver and renal function, total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, and N-terminal pro-B-type natriuretic peptide (NT-proBNP) were assessed (HITACHI 912 Analyzer, Roche Diagnostics, Germany). The estimated glomerular filtration rate (eGFR) was computed using the Chronic Kidney Disease Epidemiology Collaboration equation. Blood glycated hemoglobin A1c (HbA1c) was measured using ion-exchange high performance liquid chromatography with Bio-rad Variant Hemoglobin Testing System (Bio-Rad Laboratories, USA).

#### Echocardiographic examination

Comprehensive transthoracic echocardiography was performed using a commercially available system (Vivid-I, GE Healthcare, Milwaukee, WI). The sonographers were blinded to this study. Two-dimensional echocardiography and Doppler flow imaging were recorded from standard parasternal and apical transducer positions.

LVEF was calculated using the modified Simpson's biplane technique. The LV length was measured in an apical 4-chamber view. To facilitate application of clinical normality cut points, LV end-diastolic volume (EDV) and end-systolic volume (ESV) were indexed by BSA calculated at the study time point. LV mass was estimated from M-mode measurements by the formula:  $\text{LV mass} = 0.8 \times 1.04 \times [(EDD + IVST + PWT)^3 - EDD^3] + 0.6$ , and was indexed by BSA, where EDD is LV end-diastolic diameter, IVST is interventricular septal thickness, PWT is LV posterior wall thickness.

#### CT scans

CCTA scans were performed on dual-source CT systems (SOMATOM<sup>®</sup> Definition Flash or SOMATOM<sup>®</sup> Force, Siemens Healthineers) with the use of iodine contrast agent. Non-contrast images were routinely acquired by a prospectively electrocardiogram-triggered high-pitch spiral acquisition mode followed by contrast CT scans. Adhering to the common practice for EAT assessment in previous studies, this study utilized non-contrast cardiac CT data with the following parameters. SOMATOM<sup>®</sup> Definition Flash (256-slice CT): axial scan;

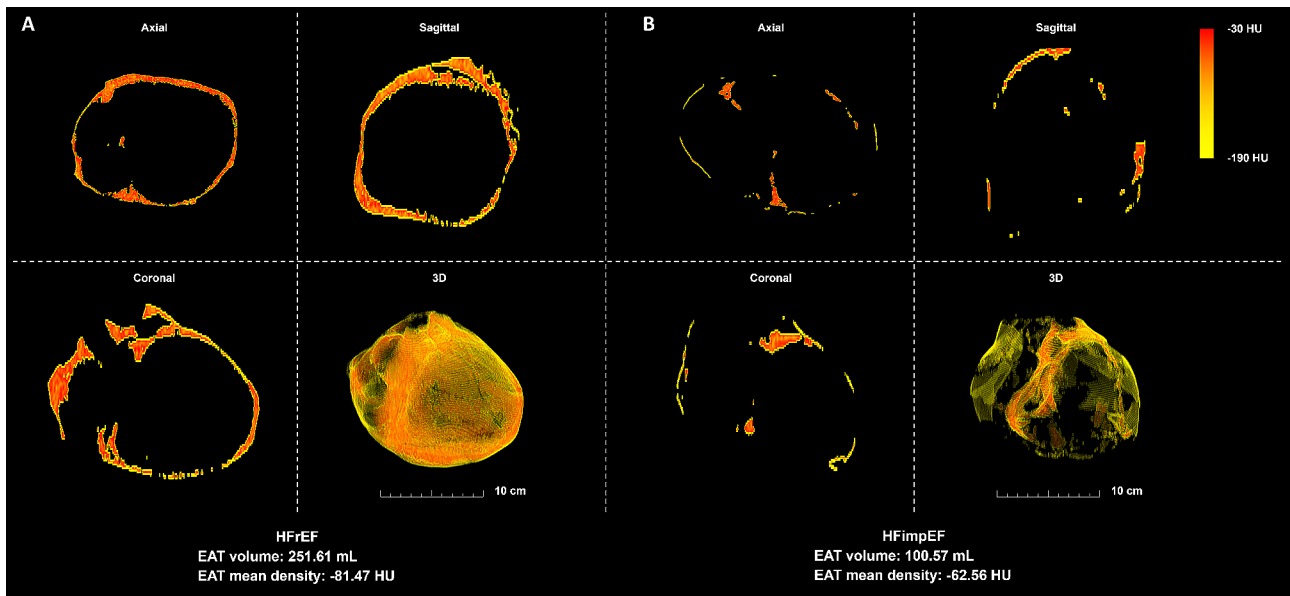
X-ray exposure times, 148 ms; tube voltage, 120 kV; tube currents, 429 mA; center of imaging window, 70% of R-R interval. SOMATOM<sup>®</sup> Force (384-slice CT): axial scan; X-ray exposure times, 285 ms; tube voltage, 120 kV; tube currents, 858 mA; center of imaging window, 70% of R-R interval. For image reconstruction, a B35f (SOMATOM<sup>®</sup> Definition Flash) or Qr36f (SOMATOM<sup>®</sup> Force) convolution kernel was used for non-contrast scans with a slice thickness of 3.0 mm and an increment of 1.5 mm. All the CT images were transferred to a dedicated workstation (Xcelera, Philips) for image post-processing.

#### EAT measurement

One observer with extensive experience in cardiac CT analysis who was blinded to the patients' information did the analysis. EAT volume was quantified on non-contrast-enhanced images using an open-source medical imaging processing software 3D Slicer (Boston, USA, 5.2.2 version). EAT was defined as the fat tissue between the outer wall of the myocardium and the visceral layer of the pericardium, which was quantified using a region of interest (ROI) manually defined by tracing the pericardium from the pulmonary artery trunk to the LV apex. Then the software reconstructed EAT into a three-dimensional region and automatically measured EAT volume and average attenuation by including contiguous three-dimensional fat voxels ranged from  $-190$  to  $-30$  Hounsfield units (HU) in the ROI as previously described [18] (Fig. 2).

#### Statistical analyses

Continuous variables were presented as median (interquartile range [IQR]) or mean  $\pm$  standard deviation (SD), and categorical data were summarized as frequencies (percentages). Normal distribution of continuous variables was evaluated by Shapiro-Wilk test. For non-normally distributed continuous variables, differences were analyzed by Mann-Whitney U test or Kruskal-Wallis test. Differences among groups were analyzed by Student's t-test or one-way analysis of variance (ANOVA). Correlation between EAT properties and changes in LVEF was determined by Spearman's correlation test. Univariate logistic regression analysis was performed to identify predictors for HFimpEF. Afterwards, multivariate regression models were constructed to interrogate the association between EAT properties and HFimpEF. Traditional risk factors, adiposity-associated index (BMI) and predictors with  $P < 0.10$  in the univariate analysis were selected as confounding factors in the multivariate analysis. In Model 1, age and sex were adjusted. In Model 2, additional adjustment was performed for smoking habits, BP, BMI, HF etiology, as well as history of myocardial infarction, hypertension and diabetes. In Model 3, we further adjusted for hemoglobin, HbA1c, triglyceride, blood



**Fig. 2** EAT on non-enhanced series of CCTA in HFrEF and HFimpEF patients. Shown are representative axial, sagittal and coronal images of EAT in patients with persistent HFrEF and HFimpEF. EAT density was converted into pseudo-color according to CT attenuation ranging from  $-190$  to  $-30$  HU. 3D visualization of EAT was performed by reconstruction of EAT volumes. A color scale bar is shown aside. **A** EAT in HFrEF; **B** EAT in HFimpEF. CCTA coronary CT angiography, EAT epicardial adipose tissue, HFimpEF heart failure with improved ejection fraction, HFrEF heart failure with reduced ejection fraction, HU Hounsfield units

urea nitrogen and eGFR. In Model 4, guideline-directed therapies including beta-blockers, angiotensin converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB), angiotensin receptor-neprilysin inhibitors (ARNI), spironolactones as well as sodium-glucose cotransporter 2 (SGLT2) inhibitors were additionally adjusted. In Model 5, baseline EDV index and ESV index were further adjusted. In these models, the association between HFimpEF and EAT volume (models with a suffix 'a') or density (models with a suffix 'b') were analyzed respectively. In Model 6, both EAT volume and density were enrolled based on Model 5.

All statistical analyses were performed using the R statistical package v.4.0.3 (R Project for Statistical Computing, Vienna, Austria). A 2-tailed  $P < 0.05$  was considered statistically significant.

## Results

### Baseline characteristics of the study population

A total of 203 HFrEF patients were finally enrolled in the study. The mean age was  $58.4 \pm 13.2$  years and 82.3% were male patients. During a median follow-up of 8.6 (4.9~13.3) months, 104 (51.2%) patients developed HFimpEF, whereas 99 (48.8%) remained persistent HFrEF. The baseline characteristics of the study population are shown in Table 1. Compared with persistent HFrEF, HFimpEF patients tended to be female, younger, non-current smokers, with higher diastolic BP and better renal function. HFimpEF subjects were less frequently with an ischemic etiology, history of revascularization

and anti-platelet therapies. Both groups received optimal medical HF therapies unless intolerance or contra-indications. There was no significant difference in BMI, systolic BP, history of type 2 diabetes, hypertension, prior myocardial infarction, atrial fibrillation, HbA1c, lipid profiles, NT-proBNP and other medical therapies between the two groups. Echocardiography analysis showed that baseline LV chamber tended to be smaller in HFimpEF compared to persistent HFrEF patients. Significant LV reverse remodeling accompanied by LVEF improvement was observed in HFimpEF patients (Supplementary Table 1).

### EAT volume and density

In the overall population, the median EAT volume was 111.51 (IQR 101.33~184.36) mL and mean EAT density was  $-76.79 \pm 6.83$  HU. EAT density was inversely correlated with EAT volume (Spearman's  $r = -0.33$ ,  $P < 0.001$ ). Compared with HFrEF patients, HFimpEF patients had lower EAT volume (115.36 [IQR 87.08~154.78] mL vs. 169.67 [IQR 137.22~218.89] mL,  $P < 0.001$ ) and higher EAT density ( $-74.92 \pm 6.84$  HU vs.  $-78.76 \pm 6.28$  HU,  $P < 0.001$ ) (Fig. 3 and Table 2). BMI-indexed EAT volume was also significantly lower in HFimpEF than HFrEF patients ( $P < 0.001$ ; Table 2 and Supplementary Figure 1).

Furthermore, correlation analyses (Fig. 4) showed that changes in LVEF were inversely correlated to EAT volume (Spearman's  $r = -0.35$ ,  $P < 0.001$ ) while positively correlated to EAT density (Spearman's  $r = 0.18$ ,  $P = 0.009$ ). Of note, EAT volume exhibited a stronger correlation with

**Table 1** Baseline demographic and clinical characteristics

	Persistent HFrEF	HFimpEF	P value
N	99	104	
Demographic characteristics and clinical measures			
Male sex	89 (89.9)	78 (75.0)	0.009
Age, years	61.56 ± 10.47	55.35 ± 14.74	0.001
Type 2 diabetes	29 (29.3)	24 (23.1)	0.396
Hypertension	53 (53.5)	49 (47.1)	0.439
Prior MI	8 (8.1)	2 (1.9)	0.089
Atrial Fibrillation	11 (11.1)	12 (11.5)	1.000
Current smokers	54 (54.5)	36 (34.6)	0.007
Body mass index, kg/m <sup>2</sup>	25.21 ± 5.08	25.01 ± 4.48	0.770
Systolic BP, mmHg	125.07 ± 20.97	127.98 ± 21.88	0.335
Diastolic BP, mmHg	74.54 ± 12.83	80.47 ± 17.56	0.007
Ischemic etiology	59 (59.6)	44 (42.3)	0.020
Laboratory values			
White blood cells, 10 <sup>9</sup> /L	7.01 ± 2.53	6.94 ± 2.04	0.825
hsCRP, mg/L	1.58 (0.69 ~ 3.80)	2.03 (0.75 ~ 4.65)	0.422
Hemoglobin, g/L	134.62 ± 20.48	139.95 ± 22.01	0.081
HbA1c, %	6.47 ± 1.13	6.21 ± 1.16	0.135
Triglyceride, mmol/L	1.34 (1.10 ~ 1.71)	1.36 (1.05 ~ 1.94)	0.479
Total cholesterol, mmol/L	4.08 ± 1.22	4.15 ± 1.04	0.708
HDL cholesterol, mmol/L	1.06 ± 0.27	1.04 ± 0.26	0.686
LDL cholesterol, mmol/L	2.55 ± 1.03	2.53 ± 0.87	0.901
BUN, mmol/L	7.67 ± 3.06	6.78 ± 2.28	0.022
Uric acid, μmol/L	412.96 ± 118.36	407.41 ± 121.97	0.750
Serum creatine, μmol/L	97.69 ± 32.29	89.04 ± 22.80	0.031
eGFR, mL/min/1.732m <sup>2</sup>	88.19 ± 16.55	94.05 ± 17.37	0.018
NT-proBNP, pg/mL	1470.0 (674.6 ~ 2842.0)	1646.0 (558.9 ~ 3535.5)	0.937
Coronary revascularization			
Revascularization	39 (39.4)	26 (25.0)	0.041
Medication use			
Aspirin	58 (58.6)	40 (38.5)	0.006
P2Y12 inhibitors	53 (53.5)	29 (27.9)	<0.001
Beta blockers	88 (88.9)	86 (82.7)	0.289
SGLT2 inhibitors	14 (14.1)	20 (19.2)	0.434
RAAS inhibitors	74 (74.7)	80 (76.9)	0.843
ARNI	27 (27.3)	30 (28.8)	0.926
ACEI	26 (26.3)	35 (33.7)	0.320
ARB	21 (21.2)	15 (14.4)	0.279
Spirolactone	71 (71.7)	79 (76.0)	0.597
Diuretics	62 (62.6)	66 (63.5)	1.000
Statins	48 (48.5)	43 (41.3)	0.378

Data are expressed as mean ± standard deviation, median (interquartile range) or number (percentage)

ACEI angiotensin-converting enzyme inhibitors, ARB angiotensin receptor blockers, ARNI angiotensin receptor-neprilysin inhibitors, BP blood pressure, BUN blood urea nitrogen, eGFR estimated glomerular filtration rate, HbA1c glycated hemoglobin A1c, HDL high-density lipoprotein, HFimpEF heart failure with improved ejection fraction, HFrEF heart failure with reduced ejection fraction, hsCRP high-sensitivity C-reactive protein, LDL low-density lipoprotein, MI myocardial infarction, NT-proBNP N-terminal pro-B-type natriuretic peptide, RAAS renin-angiotensin-aldosterone system, SGLT2 sodium-glucose cotransporter 2

LV reverse remodeling than EAT density (Supplementary Table II).

### The association between EAT volume or density and HFimpEF

Univariate regression analysis (Supplementary Table III) revealed that predictors for HFimpEF were younger age, female sex, non-current smokers, higher diastolic BP, non-ischemic etiology, better renal function, smaller LV chamber size, as well as lower EAT volume and higher EAT density.

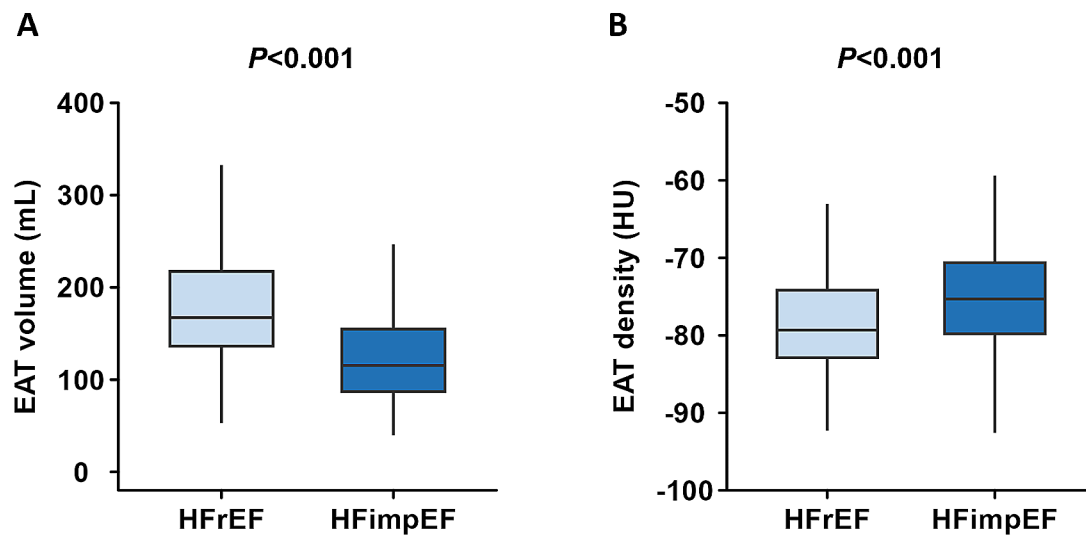
Multivariate regression analysis (Table 3) demonstrated that EAT volume and density were both significantly associated with the development of HFimpEF after adjustment for conventional risk factors, pharmacological therapies and baseline anthropometric parameters including BMI. In the full adjustment model (Model 6) that enrolled both EAT properties, EAT volume and density were both independently associated with HFimpEF after multivariate adjustment. Every 10 mL increase in EAT volume corresponded to a 11.5% decreased likelihood of HFimpEF (OR: 0.885 [95%CI 0.822 ~ 0.947]), whereas each 10 HU increase in EAT mean density was associated with an 84.5% greater incidence of HFimpEF (OR: 1.845 [95%CI 1.023 ~ 3.437]).

Furthermore, subgroup analysis (Table 4) exhibited that the associations of HFimpEF with EAT volume and density were independent of age, BMI, and HF etiology.

### Discussion

The major findings of the present study are that HF patients with lower EAT volume and higher EAT density are more likely to develop HFimpEF. EAT volume and density are independent predictors for HFimpEF, irrespective of HF etiology and BMI.

HFimpEF has been increasingly emphasized for the lower cardiovascular mortality, less re-hospitalization rate, and improved health-related life quality compared to HFrEF or HFpEF [19–21]. Existing evidence reveals that myocardial recovery from failing heart is a complex process driven by coordinated gene reprogramming, switch of cellular phenotypes and metabolic pathways [4–6]. A number of cohort studies showed that this recovery process is more readily to occur in certain clinical conditions after guideline-directed medical therapies [1, 22, 23]. Previously, we also showed that cardiometabolic factors such as insulin resistance, glycemic levels and variability, are implicated in the development of HFimpEF [24–26]. In this study, 51.2% of the hospitalized HF patients developed HFimpEF by optimal medical therapy during a median of 8.6-month follow-up. In line with previous reports, we showed by univariate analysis that predisposing factors for HFimpEF were younger age, female sex, non-current smokers, higher diastolic BP,



**Fig. 3** HFimpEF patients had lower EAT volume but higher EAT density compared with persistent HFrEF patients. Shown are EAT volume (**A**) and EAT density (**B**) in patients with persistent HFrEF and HFimpEF. Horizontal lines in the box: upper, 75% percentile; middle, median; lower, 25% percentile. Upper whisker, 95% percentile; lower whisker, 5% percentile. EAT epicardial adipose tissue, HFimpEF heart failure with improved ejection fraction, HFrEF heart failure with reduced ejection fraction, HU Hounsfield units

**Table 2** Volume and density of EAT

	Persistent HFrEF	HFimpEF	<i>P</i> value
n	99	104	
Volume, mL	169.67 (137.22~218.89)	115.36 (87.08~154.78)	<0.001
BMI-indexed volume, mL·m <sup>2</sup> /kg	6.77 (5.36~9.10)	4.63 (3.54~6.27)	<0.001
Mean density, HU	-78.76±6.28	-74.92±6.84	<0.001
SD of density, HU	32.89±2.73	32.57±2.88	0.414

Data are expressed as mean±standard deviation or median (interquartile range)

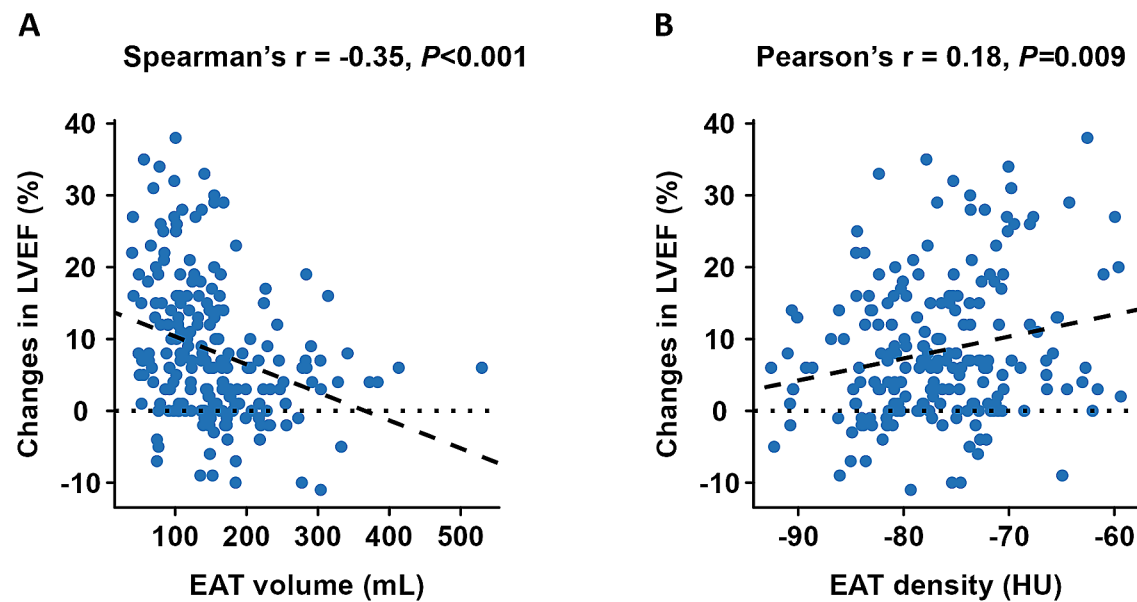
BMI body mass index, EAT epicardial adipose tissue, HFimpEF heart failure with improved ejection fraction, HFrEF heart failure with reduced ejection fraction, HU Hounsfield units, SD standard deviation

non-ischemic etiology, better renal function and smaller LV chamber size.

Myocardial function and remodeling are affected not only by systemic factors but also by local environment. EAT has been recognized as a metabolic sensor and transducer, secreting adipokines, cytokines, or pro/anti-inflammatory mediators to exert exocrine and paracrine effects on the myocardium [7, 13]. The prevailing evidence supports a role of EAT as an independent risk factor for the incidence of HF. The

risk of HF increased by 34%~43% per SD increase in EAT volume/thickness over the general population [27–29]. Additionally, HF patients with elevated EAT volume suffered a 2-fold higher all-cause mortality (HR: 2.06 [95% CI, 1.26–3.37],  $P=0.004$ ) and a 54% greater risk of HF hospitalization (HR: 1.54 [95% CI, 1.04–2.30],  $P=0.03$ ) [16]. However, the so-far understanding of the relationship between EAT and HF is mainly derived from HFpEF. Previous studies revealed that EAT volume differs between HFpEF with HFrEF patients. Compared to healthy controls, total EAT volume or thickness is higher in HFpEF but lower in HFrEF irrespective of aetiology [15, 30–33]. Pugliese et al. revealed that EAT has different impacts on HFrEF and HFpEF in terms of cardiovascular hemodynamics, metabolic profile and prognosis [31]. Reduced EAT thickness in HFrEF, in contrast to HFpEF, has been shown to be associated with elevated inflammatory response and myocardial damage characterized by higher hs-CRP, troponins as well as NT-proBNP levels [31]. However, data on EAT parameters in HFimpEF patients are still limited.

In this study, we clearly demonstrated an inverse association between EAT volume and HFimpEF after



**Fig. 4** Correlation between changes in LVEF and EAT volume or density. The dashed line indicates the predictive changes in LVEF by EAT volume (A) or density (B) using linear regression. *EAT* epicardial adipose tissue, *HU* Hounsfield units, *LVEF* left ventricular ejection fraction

adjustment for traditional risk factors. Every 10 mL increase in EAT volume corresponded to a 11.5% decreased likelihood of HFimpEF. Moreover, subgroup analysis revealed the association between EAT volume and HFimpEF persisted significant irrespective of age, general adiposity reflected by BMI, as well as the presence of ischemic etiology. These data jointly support the notion that higher EAT volume is associated with compromised development of HFimpEF. Some plausible mechanisms may provide explanation. In the setting of HF, EAT can be transformed into a hypertrophic and inflamed state, leading to sustained inflammation, fibrosis, cardiomyocyte disarray and apoptosis in the myocardium via secreting pro-inflammatory and profibrotic cytokines or mediators [7, 13]. In addition, accumulating EAT may infiltrate the contiguous myocardium, resulting in direct mechanical compression and lipotoxic effects, thereby worsening both LV diastolic and systolic function [17, 34, 35]. Indeed, an animal study performed in obese rats subjected to acute myocardial infarction showed that surgical resection of cardiac fat was associated with better LVEF compared with those without fat resection [36]. Moreover, SGLT2 inhibitors have been shown to not only reduce the quantity of EAT, but also ameliorate adipose

inflammation [7, 11], which might partly account for its salutary role in HF across the whole spectrum of EF.

On the other hand, we further revealed that higher EAT density is associated with myocardial recovery independent of EAT volume and HF etiology. Every 10 HU increase in EAT mean density was associated with an 84.5% greater incidence of HFimpEF. EAT density, measured by CT tissue attenuation, to some extent reflects the composition of EAT by adipocytes, stromal cells and infiltrated inflammatory cells [37]. Adult EAT is mainly composed of white adipose tissue (WAT) and small portion of brown adipose tissue (BAT), the latter is of smaller size, higher density, and cardioprotective effects. The proportion of BAT was shown to decrease with age or under various pathological conditions [18, 38, 39]. In the setting of HF, EAT is prone to be 'whitening' (more WAT and less BAT), expanded and inflamed, thus presenting with higher volume and lower CT attenuation [14, 17, 37]. Based on prior basic studies, CT is able to distinguish between BAT and WAT based on CT attenuation values and it is rational to hypothesize that EAT with higher density represents higher proportion of BAT, which confers beneficial paracrine and cardiometabolic effects, and facilitates myocardium structural and functional restoration [14, 38]. Actually, current evidence suggests 're-browning'



**Table 3** Multivariate regression analysis

	EAT volume (per 10 mL)		EAT mean density (per 10 HU)	
	OR (95% CI)	P value	OR (95% CI)	P value
Model 1a	0.897 (0.851~0.941)	<0.001	–	–
Model 1b	–	–	2.463 (1.558~4.032)	<0.001
Model 2a	0.874 (0.820~0.926)	<0.001	–	–
Model 2b	–	–	2.334 (1.423~3.973)	0.001
Model 3a	0.880 (0.822~0.937)	<0.001	–	–
Model 3b	–	–	2.314 (1.369~4.075)	0.002
Model 4a	0.878 (0.818~0.936)	<0.001	–	–
Model 4b	–	–	2.206 (1.278~3.969)	0.006
Model 5a	0.874 (0.812~0.934)	<0.001	–	–
Model 5b	–	–	2.219 (1.270~4.044)	0.007
Model 6	0.885 (0.822~0.947)	<0.001	1.845 (1.023~3.437)	0.046

Model 1, adjustment for age and sex;

Model 2, additional adjustment for smoking habits, BP, BMI, HF etiology, history of myocardial infarction, hypertension and diabetes;

Model 3, additional adjustment for hemoglobin, HbA1c, triglyceride, blood urea nitrogen and estimated glomerular filtration rate;

Model 4, additional adjustment for use of beta-blockers, ACEI, ARB, ARNI, spironolactones as well as SGLT2 inhibitors;

Model 5, additional adjustment for baseline EDV index and ESV index;

In these models, the association between HFimpEF and EAT volume (models with a suffix 'a') or density (models with a suffix 'b') were analyzed respectively;

Model 6, both EAT volume and density were enrolled based on Model 5

ACEI angiotensin-converting enzyme inhibitors, ARB angiotensin receptor blockers, ARNI angiotensin receptor-neprilysin inhibitors, BMI body mass index, BP blood pressure, CI confidence interval, EAT epicardial adipose tissue, EDV end-diastolic volume, ESV end-systolic volume, HbA1c glycated hemoglobin A1c, HF heart failure, HFimpEF heart failure with improved ejection fraction, HU Hounsfield units, OR odds ratio, SGLT2 sodium-glucose cotransporter 2

of EAT may improve the hypoxic and inflammatory microenvironment, favoring a better outcome [17]. From another perspective, EAT density is reflective of both local and systemic inflammatory status [14, 40, 41]. In inflamed adipose tissue, local adipogenesis is inhibited, thereby leading to a shift towards higher tissue density from the lipid phase to the aqueous phase [41]. Thus, higher EAT density is indicative of less adipocyte hypertrophy and hyperplasia, and more content of water, fibrosis and inflammatory cells [41]. Previous studies displayed conflicting results on the association between EAT density and different types of cardiovascular diseases [37, 40, 41]. According to the findings in our study, EAT density was significantly higher in

**Table 4** Subgroup analysis

Parameter	Subgroups	OR (95% CI)	P for interaction
EAT volume (per 10 mL)	Age	< 60 years	0.793 (0.651~0.917)
		≥ 60 years	0.821 (0.720~0.914)
	Etiology	Non-ischemic	0.778 (0.662~0.888)
		Ischemic	0.887 (0.801~0.972)
EAT mean density (per 10 HU)	BMI	< 24 kg/m <sup>2</sup>	0.546 (0.340~0.738)
		≥ 24 kg/m <sup>2</sup>	0.875 (0.774~0.967)
	Age	< 60 years	17.353 (3.267~159.434)
		≥ 60 years	2.031 (0.896~4.873)
	Etiology	Non-ischemic	2.491 (0.993~6.908)
		Ischemic	2.710 (1.111~7.711)
	BMI	< 24 kg/m <sup>2</sup>	3.639 (1.119~15.993)
		≥ 24 kg/m <sup>2</sup>	2.488 (0.981~6.865)

BMI body mass index, CI confidence interval, EAT epicardial adipose tissue, HU Hounsfield units, OR odds ratio

HFimpEF than HFrefEF patients. Hence, it is reasonable to propose that moderate inflammation in EAT might provide salutary effects for myocardial reparation and LV reverse remodeling. However, these hypotheses await to be validated and in-depth research.

**Limitations**

Our findings should be interpreted in the context of the following limitations. First, this study is a retrospective analysis from a single center with relatively small size. Second, anthropometric parameters such as waist circumference and waist-to-hip ratio were not recorded though the association between EAT and HF has been previously shown to be independent of global adiposity [27]. Third, the proportion of active BAT can only be accurately measured by positron emission tomography (PET) acquisition rather than CT scans. Therefore, the extent to which BAT exerts beneficial effect cannot be evaluated from existing data and is our important future goal. Fourth, hard endpoints were not recorded due to the study design. Prospective studies are warranted to analyze the causal link between EAT and the development of HFimpEF.

## Conclusions

In conclusion, our findings suggest that lower EAT volume and higher EAT density are associated with the development of HFimpEF independent of BMI and HF etiology. Therapies targeted at reducing EAT quantity and improving its quality might provide favorable effects on myocardial recovery in HF patients.

## Abbreviations

ACEI	Angiotensin converting enzyme inhibitors
ANOVA	Analysis of variance
ARB	Angiotensin receptor blockers
ARNI	Angiotensin receptor-neprilysin inhibitors
BAT	Brown adipose tissue
BMI	Body mass index
BP	Blood pressure
BSA	Body surface area
CCTA	Coronary CT angiography
EAT	Epicardial adipose tissue
EF	Ejection fraction
eGFR	Estimated glomerular filtration rate
EDD	End-diastolic diameter
EDV	End-diastolic volume
ESV	End-systolic volume
HbA1c	Glycated hemoglobin A1c
HDL	High-density lipoprotein
HF	Heart failure
HFimpEF	Heart failure with improved ejection fraction
HFpEF	Heart failure with preserved ejection fraction
HFrfEF	Heart failure with reduced ejection fraction
HU	Hounsfield units
IQR	Interquartile range
IVST	Interventricular septal thickness
LDL	Low-density lipoprotein
LV	Left ventricular
LVEF	Left ventricular ejection fraction
NT-proBNP	N-terminal pro-B-type natriuretic peptide
PET	Positron emission tomography
PWT	Posterior wall thickness
ROI	Region of interest
SD	Standard deviation
SGLT2	Sodium-glucose cotransporter 2
WAT	White adipose tissue

## Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s12933-024-02376-y>.

Supplementary Material 1.

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None.

## Author contributions

CY and XW performed study design, data analysis and data interpretation. CY, JQ and XW performed manuscript writing. CY, JQ, GT, SF, HY, AA, ST, XW, RY and XW performed data collection. CY, RZ, LL and XW performed manuscript revision. All authors reviewed the manuscript.

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## Data availability

No datasets were generated or analysed during the current study.

## Declarations

### Ethics approval and consent to participate

The study was approved by the Shanghai Ruijin Hospital ethics committee, and written informed consent was obtained from all patients.

### Consent for publication

Not applicable.

### Competing interests

The authors declare no competing interests.

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