Correlation between Low Amount of Epicardial Adipose Tissue and the Severity of Right Ventricular Dysfunction in Patients with Nonischemic Heart Failure with Reduced Ejection Fraction

Akiko Tanihata, Shoichi Ehara, Ryoko Kitada, Hirotoshi Ishikawa, Toshitake Yoshida, Hiroya Hayashi, Yumi Yamaguchi, Atsushi Shibata, Yasuhiro Izumiya, Daiju Fukuda

Citation	Osaka City Medical Journal. 68(2); 61-72
Issue Date	2022-12
Type	Journal Article
Textversion	Publisher
Rights	© Osaka City Medical Association. https://osakashi-igakukai.com/.

Akiko Tanihata et al. Correlation between Low Amount of Epicardial Adipose Tissue and the Severity of Right Ventricular Dysfunction in Patients with Nonischemic Heart Failure with Reduced Ejection Fraction. *Osaka City Medical Journal.* 2022, 68, 2, 61-72.

Osaka City Med. J. Vol. 68, 61-72, 2022

Correlation between Low Amount of Epicardial Adipose Tissue and the Severity of Right Ventricular Dysfunction in Patients with Nonischemic Heart Failure with Reduced Ejection Fraction

Akiko Tanihata[1)], Shoichi Ehara[2)], Ryoko Kitada[2)], Hirotoshi Ishikawa[2)], Toshitake Yoshida[1)], Hiroya Hayashi[1)], Yumi Yamaguchi[2)], Atsushi Shibata[2)], Yasuhiro Izumiya[2)], and Daiju Fukuda[2)]

Department of Cardiovascular Medicine[1)],
Osaka City University Graduate School of Medicine; and
Department of Cardiovascular Medicine[2)],
Osaka Metropolitan University Graduate School of Medicine

Abstract

Background

Although epicardial adipose tissue (EAT) volume is associated with coronary artery disease and atrial fibrillation, the clinical role of EAT in heart failure (HF) remains controversial. In patients with HF with reduced ejection fraction (HFrEF), right ventricular (RV) dysfunction is associated with impaired functional capacity. This study aimed to investigate the relationship between the EAT volume and RV systolic function in patients with HFrEF.

Methods and Results

A total of 100 consecutive patients with nonischemic HF who had undergone cardiac magnetic resonance imaging and computed tomography were enrolled. First, patients were categorized based on the left ventricular (LV) EF; patients with LVEF ≧50% and LVEF <50% were classified into the HF with preserved EF (HFpEF) (n=14) and HFrEF (n=86) groups, respectively. Then, the HFrEF group was further divided into the HFrEF with RV dysfunction (RVEF <45%, n=54) and HFrEF without RV dysfunction (RVEF ≧45%; n=32) groups. The EAT volume indexed to body surface area (BSA) in the HFrEF with RV dysfunction group was significantly lower than that in the other groups. In the HFrEF group, EAT volume indexed to BSA was positively correlated with RVEF ($r=0.28$, $p<0.01$) but not with LVEF. Multivariate analysis revealed that LVEF and EAT volume indexed to BSA were independent factors associated with HFrEF with RV dysfunction.

Conclusions

This study demonstrated that HFrEF patients with RV dysfunction had less EAT compared to HFpEF patients, and less amount of EAT was related to the severity of RV dysfunction in HFrEF.

Key Words: Epicardial adipose tissue, Heart failure, Right ventricular failure, Magnetic resonance imaging

Received February 21, 2022; accepted June 14, 2022.

Correspondence to: Shoichi Ehara, MD.
Department of Cardiovascular Medicine, Osaka Metropolitan University Graduate School of Medicine, 1-4-3 Asahimachi, Abeno-ku, Osaka 545-8585, Japan
Tel: +81-6-6645-3801; Fax: +81-6-6646-6808
E-mail: ehara@omu.ac.jp

Introduction

The concept of cardiac adiposity as a novel cardiovascular risk factor has recently received increasing attention. Epicardial adipose tissue (EAT) is a unique and multifaceted visceral fat depot and has anatomic and biomolecular relationship with the heart. The functional and anatomic proximity of EAT to the coronary artery and myocardium enables endocrine, paracrine, and vasocrine effects on the heart. Previous studies have shown that EAT volume is associated with obesity[1], metabolic syndrome[2,3], insulin resistance[4], atrial fibrillation[5,6], and coronary artery disease[7,8]. However, the clinical role of EAT in heart failure (HF) remains controversial[9]. This confusion may be attributed to the heterogeneity of HF in terms of classification, stage, and severity.

It has been proposed that left ventricular (LV) remodeling in HF with reduced ejection fraction (HFrEF) is driven by the progressive loss of cardiomyocytes, which results from ischemia, infection, or toxicity[10]. Although nonischemic HFrEF, especially dilated cardiomyopathy, is a primary heart muscle disease characterized by LV cavity enlargement and impaired contractility, right ventricular (RV) systolic dysfunction is frequently observed during the initial evaluation. In patients with HFrEF, RV systolic dysfunction is associated with impaired functional capacity and is a key factor in determining prognosis[11]. However, most EAT-related studies have analyzed only LV function and paid less attention to RV function[12-14]. One of the reasons is that the RV has a complex shape, and it is difficult to estimate RV volume and function.

Cardiac magnetic resonance (CMR) imaging is the most accurate method for evaluating RV volume and function[15]. Furthermore, multidetector computed tomography (MDCT) can provide a more accurate and volumetric measurement of EAT compared with echocardiography. This study aimed to compare the EAT volume among patients with nonischemic HFrEF, patients with preserved ejection fraction (HFpEF), and control subjects, and to investigate the relationship between the EAT volume and RV systolic function in patients with nonischemic HFrEF.

Methods

The study was approved by the hospital ethics committee, and informed consent of patients was obtained according to the institutional review board policies regarding hospital administration (approval no.3785).

Study population

This single-center retrospective observational study enrolled 100 consecutive patients with newly diagnosed nonischemic HF who visited our institution for the evaluation of cardiac dysfunction or management of HF and underwent CMR imaging and MDCT between September 2017 and April 2021. To be diagnosed with HF, all patients had to satisfy two major or one major and two minor Framingham criteria[16]. The exclusion criteria were as follows: i) significant coronary artery disease (defined as the presence of ≧70% luminal stenosis in an epicardial coronary artery or any history of myocardial infarction or coronary revascularization), ii) severe valvular heart disease, iii) infiltrative cardiomyopathy, iv) sarcoidosis, v) amyloidosis, vi) hypertrophic cardiomyopathy, vii) myocarditis, viii) permanent pacemaker, implantable cardiac defibrillator, or cardiac resynchronization therapy, ix) uncontrolled insulin dependent diabetes mellitus, x) severe renal dysfunction with estimated glomerular filtration rate <30 mL/min/1.73m^2. First, patients were categorized based on the LV ejection fraction (LVEF) measured by CMR; patients with LVEF ≧50% and LVEF <50% were classified into the HFpEF and HFrEF groups, respectively. The HFrEF group was then further

divided into the HFrEF with RV dysfunction (RVEF <45%) and HFrEF without RV dysfunction (RVEF ≧45%) groups[17]. The HFrEF group was treated with beta-blockers, angiotensin-converting enzyme inhibitors, or angiotensin Ⅱ receptor blockers unless contraindicated. Furthermore, we included 50 individuals matched for age, sex, and body mass index (BMI), including 35 men and 15 women with a mean age of 57±12 years and BMI of 23.3±4.0, as controls to evaluate EAT volume. The control group satisfied the following criteria: normal physical examination; normal electrocardiographic findings; no significant coronary stenosis on MDCT; no history of HF, myocardial infarction, or coronary revascularization; and normal 2D echocardiographic and Doppler examination results.

Data on age, sex, and the presence of risk factors (such as smoking and hypertension, as defined by the Joint National Committee Ⅶ; diabetes mellitus, as defined by the World Health Organization study group; or dyslipidemia, as defined by the Japan Atherosclerosis Society guidelines) were also collected.

CMR image acquisition and analysis

CMR images were acquired using a 1.5-T MR imager (Achieva, Philips Medical Systems, Best, the Netherlands) with a 32-element cardiac coil. Cine MR studies were conducted using steady-state free-precession sequence at the shortest possible repetition/echo time and at a flip angle of 55° or 60° along the LV vertical long-axis. By presenting a 4-chamber view and a sequential 10-mm short-axis (no gap) from the aortic valve ring to the apex, these studies allowed for the evaluation of structural and functional assessment.

LVEF and RVEF were calculated by short-axis cine MR imaging, performed under clinically stable conditions, using Simpson's method[15]. LV and RV volumes were quantified by planimetry of the end-diastolic and -systolic endocardial borders on short-axis cine CMR images acquired from base to apex, and were indexed to body surface area (BSA). EF was calculated as the difference between end-systolic volume and end-diastolic volume divided by end-diastolic volume. CMR analyses were performed by an experienced physician (R.K) who was blinded to the clinical information using an offline workstation (View Forum, Philips Medical Systems).

Acquisition of CT data for the assessment of EAT

All MDCT scans were performed using a 64-slice CT scanner (LightSpeed VCT VISION, GE Healthcare Japan Co, Tokyo, Japan). Images were acquired during a single breath hold using prospective ECG gating with imaging triggered at 75% of the R-R interval (collimation, 64×0.625 mm; tube voltage, 120 kV; gantry rotation time, 350 ms; tube current, 200 mA). Reconstructed axial images of 2.5-mm thickness were transferred to an offline workstation (Synapse Vincent, Fujifilm Medical Co, Tokyo, Japan) for image post-processing and analysis. The pericardium counter was manually traced on each transaxial CT slice, followed by automated processing of all continuous voxels with a density range of −200 to −30 Hounsfield units (HU) within the pericardial sac. The upper border and lower border of EAT were considered at the bifurcation of the pulmonary trunk and at the LV apex, respectively. A region of interest was placed within the visceral epicardium to determine EAT area, and the total EAT volume was calculated as the sum of the EAT area on each slice multiplied by the thickness and number of slices[5]. EAT volumes were indexed to BSA or BMI. EAT volumes were analyzed by an experienced physician blinded to other information (T.Y).

Clinical measurements

In patients with HF, baseline clinical parameters were obtained from hospital records, including

laboratory analyses [serum brain natriuretic peptide (BNP) and high sensitivity C-reactive protein levels] at hospital discharge. The LV diastolic function (mitral peak E and A velocities, E/A ratio, e', and E/e' ratio, and deceleration time) and left atrial volume were assessed by echocardiography performed under clinically stable conditions.

Statistical analyses

Continuous variables are presented as mean±standard deviation for normally distributed data and as median and interquartile range for non-normally distributed data. BNP level data were not normally distributed; therefore, log-transformed values of BNP level were used for all analyses. Continuous variables were compared among the three groups using one-way analysis of variance (ANOVA), followed by a multiple comparison using post-hoc Tukey test. Categorical variables were compared using Pearson's χ^2 test. Correlations among continuous variables were assessed using the Spearman rank-correlation coefficient. Multivariate logistic regression analyses were performed to identify independent factors associated with HFrEF with RV dysfunction. Univariate predictors with a p value <0.10 were included in the multivariate model. A two-tailed p value <0.05 was considered statistically significant. All statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (the R Foundation for Statistical Computing, Vienna, Austria). More precisely, it is a modified version of R designed to add statistical functions frequently used in biostatics.

Results

A total of 100 patients were classified into the HFpEF (n=14, 14%) and HFrEF (n=86, 86%) groups. In the HFrEF group, there were 54 patients (63%) with RV dysfunction (RVEF <45%, HFrEF with RV dysfunction group) and 32 patients (37%) without RV dysfunction (RVEF ≧45%, HFrEF without RV dysfunction group). The interobserver variabilities for LVEF and RVEF measurements performed in a random sample of patients were 4.5±1.6% (r^2=0.995, p<0.0001) and 6.2±4.9% (r^2=0.995, p<0.001), respectively. The intraobserver variabilities were 2.8±2.2% (r^2=1, p< 0.0001) and 2.8±1.9% (r^2=0.997, p<0.0001), respectively. Table 1 shows the baseline clinical characteristics, echocardiographic data, and CMR data in the HFpEF, HFrEF with RV dysfunction, and HFrEF without RV dysfunction groups. There were no significant differences among the three groups regarding age, gender, BMI, and coronary risk factors except diabetes mellitus. The HFrEF with RV dysfunction group had significantly lower systolic blood pressure and higher heart rates than the HFrEF without RV dysfunction or the HFpEF group. Regarding echocardiographic parameters of LV diastolic function, the HFrEF with RV dysfunction group had significantly higher E/A ratio and lower peak A velocity and deceleration time than the HFrEF without RV dysfunction group. The HFrEF group showed significantly higher LV end-diastolic and LV end-systolic volume index and lower LVEF than the HFpEF group. The HFrEF with RV dysfunction group had significantly higher RV end-diastolic and RV end-systolic volume index and lower RVEF than the HFrEF without RV dysfunction group. Medications at discharge were significantly different among the three groups.

Figure 1 compares EAT volume and EAT volume indexed to BSA or BMI among the HFpEF, HFrEF, and control groups. The EAT volume in the HFrEF group was significantly lower than that in the HFpEF group (ANOVA: p<0.05; Fig 1A). The EAT volume indexed to BSA or BMI in the HFrEF group was also significantly lower than that in the HFpEF group (indexed to BSA, ANOVA: p

Table 1. Baseline characteristics

	HFpEF (n=14)	HFrEF without RV dysfunction (n=32)	HFrEF with RV dysfunction (n=54)	p
Age, years	63±18	60±16	57±14	0.37
Men, n (%)	9 (64%)	19 (59%)	35 (65%)	0.8
Body mass index, kg/m^2	24.6±3.5	23.2±4.1	22.2±4.3	0.25
Hypertension, n (%)	7 (50%)	15 (47%)	21 (39%)	0.66
Dyslipidemia, n (%)	5 (36%)	12 (38%)	11 (20%)	0.2
Diabetic mellitus, n (%)	0 (0%)	11 (34%)	10 (19%)	<0.05
Current Smoking, n (%)	6 (43%)	5 (16%)	14 (26%)	0.13
Systolic blood pressure, mm Hg	113.3±14.4	120.2±18.9	108.5±17.7	<0.05
Diastolic blood pressure, mm Hg	78.8±18.0	83.4±17.9	78.2±16.8	0.38
Heart rate, bpm	63.5±11.6	70.6±14.3	75.3±16.5	<0.05
Atrial fibrillation, n (%)	4 (29%)	3 (9%)	8 (15%)	0.28
Laboratory data				
Hemoglobin, g/dL	13.4±1.7	13.3±3.1	14.1±2.2	0.32
Hemoglobin A1c, mg/dL	5.7±0.4	6.0±0.6	6.2±1.6	0.4
BNP, pg/mL	180±211	160±184	249±235	0.16
Log BNP	1.93±0.60	1.96±0.49	2.18±0.47	0.07
C-reactive protein, mg/dL	0.16±0.18	0.17±0.30	0.13±0.17	0.75
Echocardiographic parameters				
Left atrial volume, mL	66.1±23.9	59.6±22.6	65.7±23.4	0.46
Peak E velocity, cm/s	74.6±20.1	63.1±23.4	75.5±24.6	0.06
Peak A velocity, cm/s	86.3±28.63	70.0±21.6	58.5±19.6	<0.001
E/A ratio	0.92±0.48	0.95±0.47	1.39±0.75	<0.05
è, cm/s	4.8±2.2	4.6±1.9	4.8±2.0	0.9
E/è ratio	19.1±12.9	14.8±4.8	18.1±9.7	0.19
Deceleration time, msec	245±98	197±76	160±60	<0.001
Moderate				
Mitral valve regurgitation	2 (14%)	6 (19%)	12 (22%)	0.83
Aortic valve regurgitation	0 (0%)	1 (3%)	0 (0%)	-
Tricuspid valve regurgitation	1 (7%)	0 (0%)	2 (4%)	-
CMR parameters				
LV ejection fraction, %	59.6±7.8	31.1±7.8	24.4±9.0	<0.001
LV EDVI, mL/m^2	78.7±20.1	124.9±32.9	135.9±45.4	<0.001
LV ESVI, mL/m^2	32.7±12.4	88.0±30.3	104.9±42.2	<0.001
RV ejection fraction, %	52.8±13.5	53.0±5.9	31.7±8.7	<0.001
RV EDVI, mL/m^2	89.6±35.7	68.7±14.3	101.7±38.3	<0.001
RV ESVI, mL/m^2	45.6±29.5	37.1±29.0	71.1±34.4	<0.001
Medication at discharge				
β blocker, n (%)	9 (64%)	28 (88%)	50 (93%)	<0.05
ACE inhibitors/ARB, n (%)	10 (71%)	25 (78%)	43 (80%)	0.75
MRB, n (%)	4 (29%)	18 (56%)	38 (70%)	<0.05
Tolvaptan, n (%)	2 (14%)	1 (3%)	4 (7%)	0.40
Loop diuretics, n (%)	8 (57%)	15 (47%)	38 (70%)	0.09

Values are mean±SD, n (%), or median (interquartile range). HFpEF indicates heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; RV, right ventricular; BNP, brain natriuretic peptide; CMR, cardiac magnetic resonance; LV, left ventricular; EDVI, end-diastolic volume index; ESVI, end-systolic volume index; ACE, angiotensin converting enzyme; ARB, angiotensin Ⅱ type 1 receptor blockers; and MRB, mineralocorticoid receptor blocker.

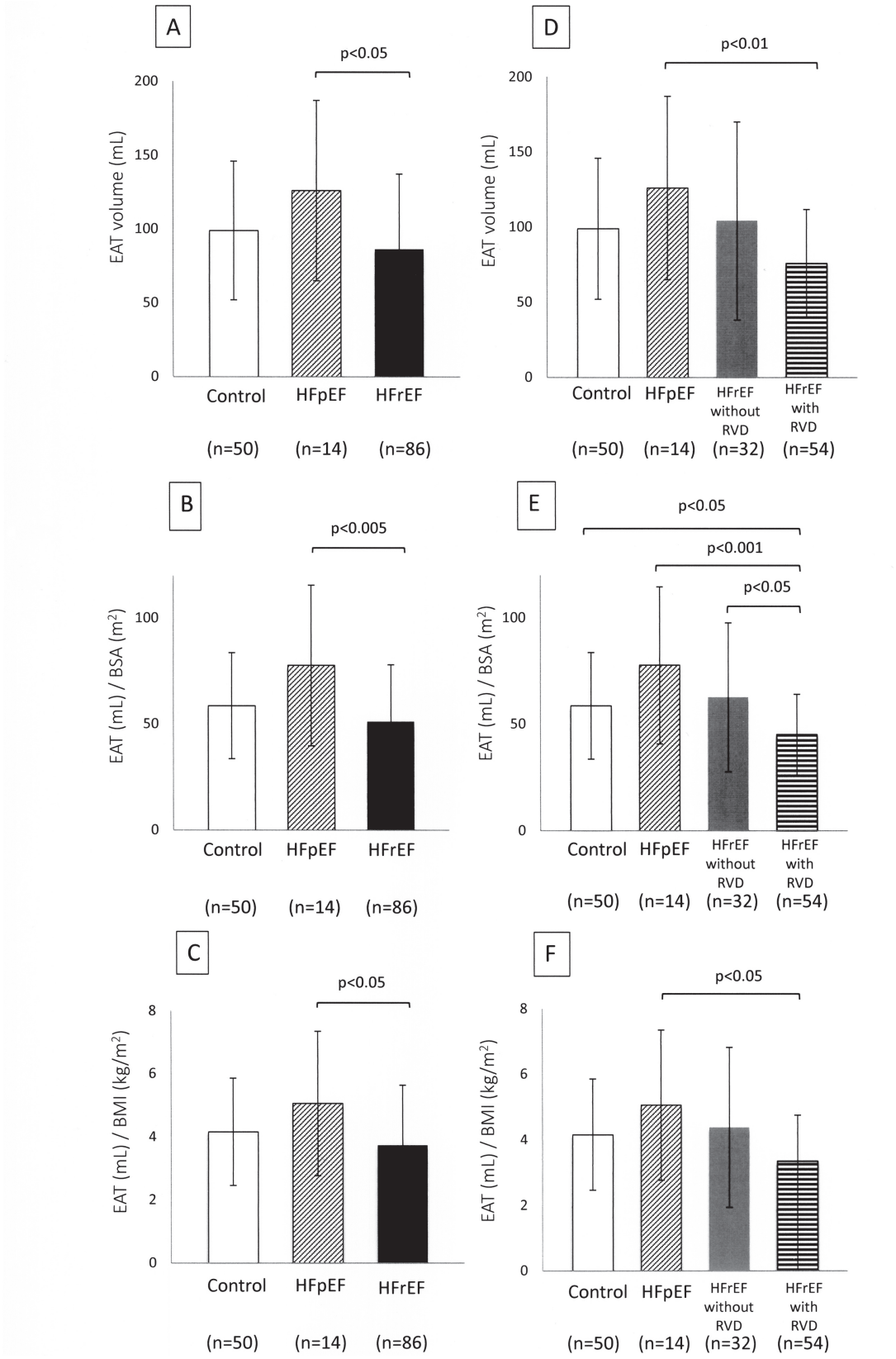

Figure 1. (A) EAT volume, (B) EAT volume indexed to BSA, and (C) EAT volume indexed to BMI in the HFpEF, HFrEF, and control groups. (D) EAT volume, (E) EAT volume indexed to BSA, and (F) EAT volume indexed to BMI in the HFpEF, HFrEF without RV dysfunction, HFrEF with RV dysfunction, and control groups. EAT, epicardial adipose tissue; BSA, body surface area; BMI, body mass index; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; and RVD, right ventricular dysfunction.

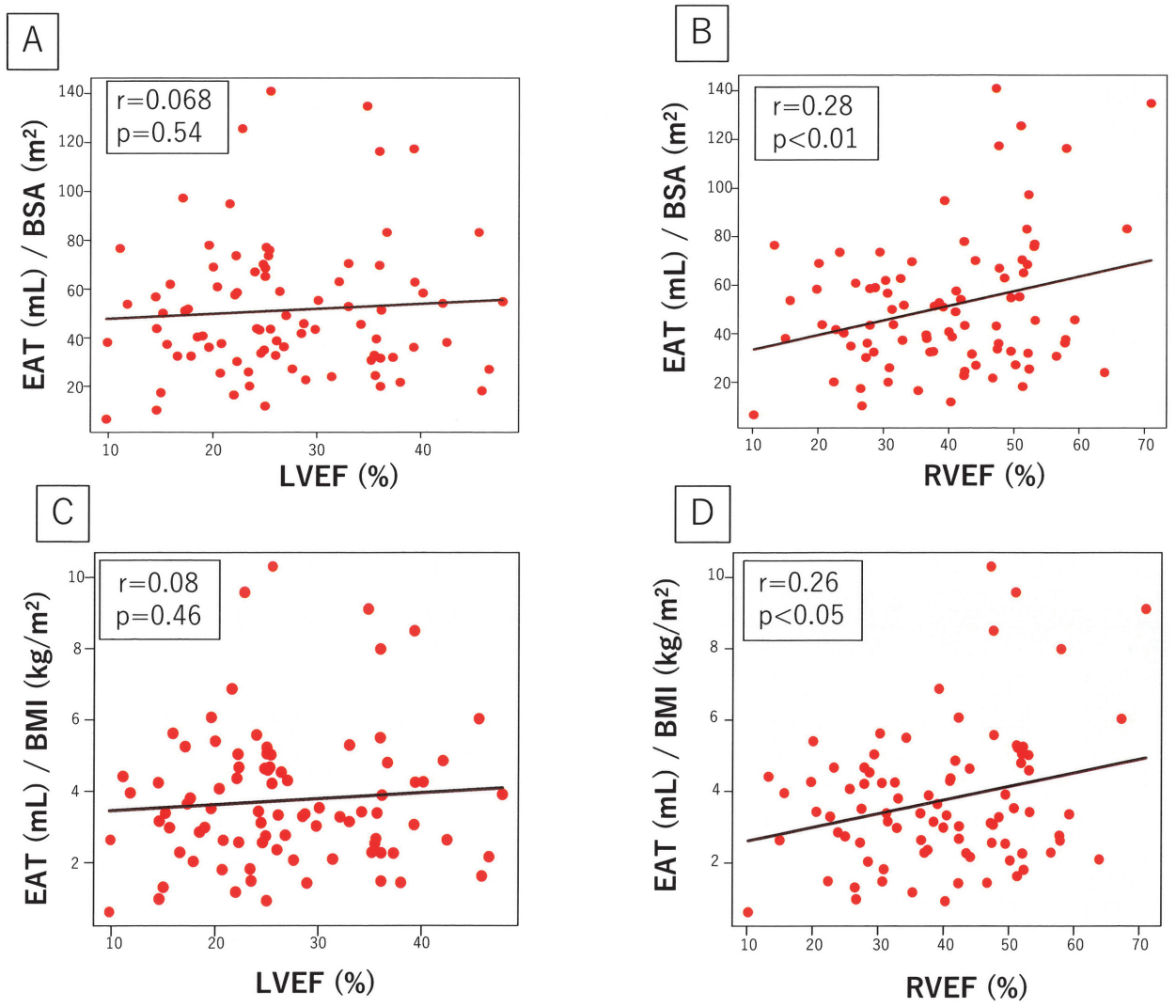

Figure 2. In the HFrEF group, the correlation of EAT volume indexed to BSA or BMI with LVEF or RVEF. (A) EAT volume indexed to BSA vs LVEF, (B) EAT volume indexed to BSA vs RVEF. (C) EAT volume indexed to BMI vs LVEF, (B) EAT volume indexed to BMI vs RVEF. HFrEF, heart failure with reduced ejection fraction; EAT, epicardial adipose tissue; BSA, body surface area; BMI, body mass index; LVEF, left ventricular ejection fraction; and RVEF, right ventricular ejection fraction.

Table 2. Univariate and multivariate analyses for association with HFrEF with RV dysfunction in patients with HF

	Univariate analysis			Multivariate analysis		
Factors	OR	95% CI	p-value	OR	95% CI	p-value
Systolic blood pressure	0.97	0.95-0.99	<0.05			
Log BNP	2.62	1.13-6.1	<0.05			
Deceleration time	0.99	0.98-1.00	<0.005			
LV ejection fraction	0.90	0.86-0.94	<0.001	0.90	0.84-0.95	<0.001
EAT volume indexed to BSA	0.97	0.96-0.99	<0.001	0.97	0.95-0.99	<0.01

HFrEF indicates heart failure with reduced ejection fraction; RV, right ventricular; HF, heart failure; BNP, brain natriuretic peptide; LV, left ventricular; EAT, epicardial adipose tissue; BSA, body surface area; OR, odds ratio; and CI, confidence interval.

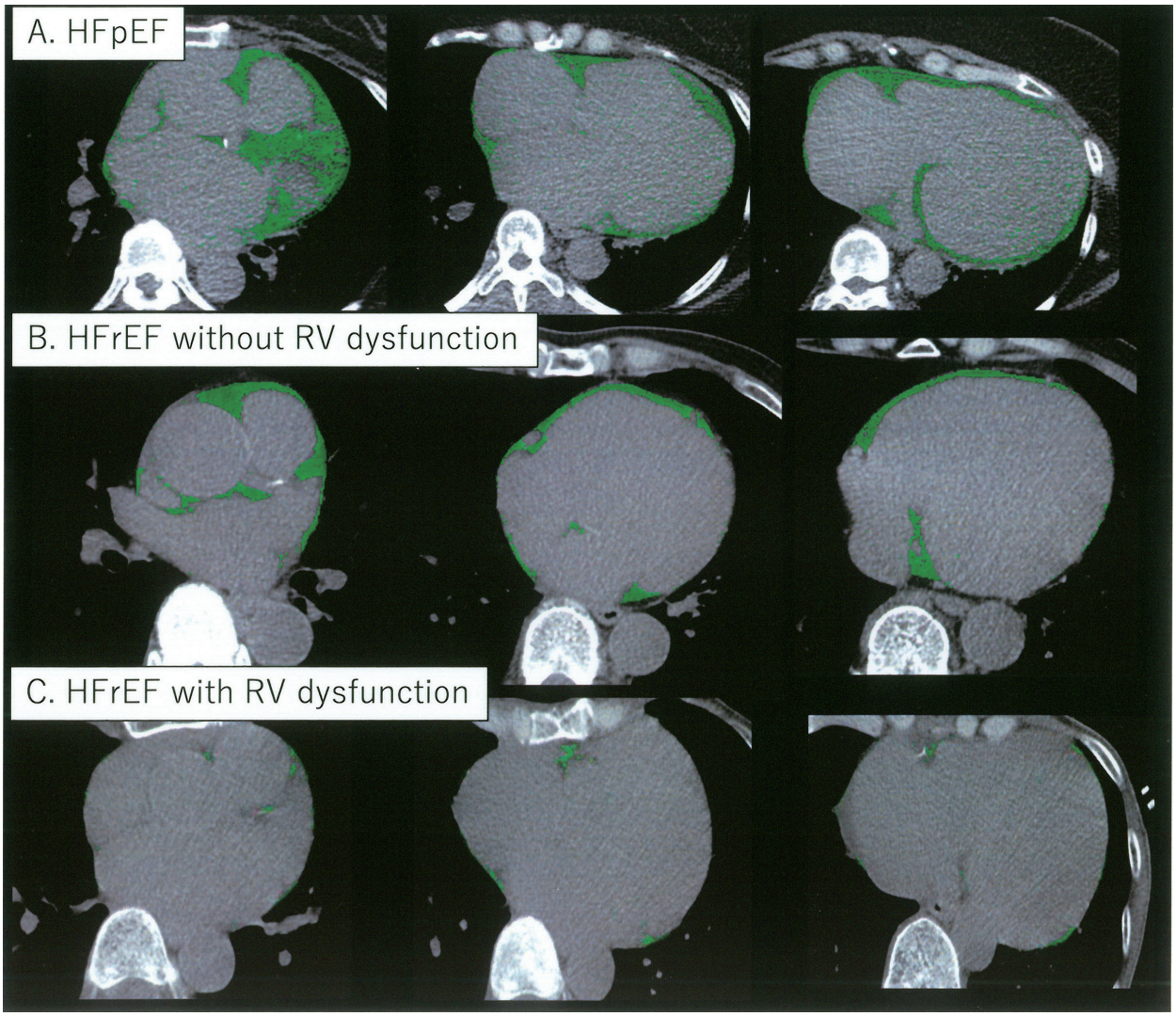

Figure 3. CT showing EAT in representative cases of HFpEF, HFrEF without RV dysfunction, and HFrEF with RVD. (A) CT showing abundant EAT surrounding the heart in a patient with HFpEF. (B) CT showing intermediate amount of EAT surrounding the heart in a patient with HFrEF without RVD. (C) CT showing very little EAT surrounding the heart in a patient with HFrEF with RVD. CT, computed tomography; EAT, epicardial adipose tissue; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; and RVD, right ventricular dysfunction.

<0.005; indexed to BMI, ANOVA: $p<0.05$, Fig 1B and C). Moreover, the EAT volume in the HFrEF with RV dysfunction group was significantly lower than in the HFpEF group (HFrEF with RV dysfunction, 75.57±35.7 mL; HFrEF without RV dysfunction, 104.1±66.1 mL, HFpEF, 126.0±61.4 mL; and controls, 99.0±47.2 mL; ANOVA: $p<0.005$; HFrEF with RV dysfunction vs HFpEF, $p<0.01$; Fig. 1D). The EAT volume indexed to BSA in the HFrEF with RV dysfunction group was significantly lower than that in the other groups (HFrEF with RV dysfunction, 44.70±19.2 mL/m^2; HFrEF without RV dysfunction, 62.0±35.2 mL/m^2, HFpEF, 77.9±38.0 mL/m^2; and controls, 58.6±25.0 mL/m^2; ANOVA: $p<0.001$; HFrEF with RV dysfunction vs HFrEF without RV dysfunction, $p<0.05$; and HFrEF with RV dysfunction vs HFpEF, $p<0.001$; Fig 1E). There was no significant difference in EAT volume and index between the HFpEF and control groups. As shown in Figure 2, the EAT volume indexed to BSA or BMI in the HFrEF group was positively correlated with RVEF (indexed to BSA, r=

0.28, $p<0.01$; indexed to BMI, $r=0.26$, $p<0.05$; Fig 2B and D), but not with LVEF (indexed to BSA, $r=0.068$, $p=0.54$; indexed to BMI, $r=0.08$, $p=0.46$; Fig 2A and C). In contrast, the EAT volume indexed to BSA or BMI in the HFpEF group was not significantly correlated with LVEF or RVEF. In patients with HF, univariable and multivariable analyses were performed to identify the independent factors associated with HFrEF with RV dysfunction (Table 2). Multivariable analysis revealed that LVEF and EAT volume indexed to BSA were independent factors associated with HFrEF with RV dysfunction. Figure 3 shows representative CT images assessing EAT in the HFpEF, HFrEF without RV dysfunction, and HFrEF with RV dysfunction groups. Figure 3-A shows abundant EAT surrounding the heart in a patient with HFpEF. In contrast, Figure 3-C and Figure 3-B show very little EAT in an HFrEF patient with RV dysfunction and intermediate amount of EAT in an HFrEF patient without RV dysfunction, respectively.

Discussion

To the best of our knowledge, this is the first study to investigate the correlation between the amount of EAT and RV function in patients with HFrEF. The major finding of this study was that HFrEF patients, especially those with RV dysfunction, had less EAT volume index compared to HFpEF patients or control patients despite similar BMI. Furthermore, the EAT volume index in the HFrEF group was positively correlated with RVEF but not LVEF. Multivariable analysis revealed that EAT volume index was an independent factor associated with HFrEF with RV dysfunction.

Some studies have shown that EAT is significantly reduced in patients with HFrEF compared to that in the healthy controls[12-14]. Our data support those findings. The association between EAT and mechanisms responsible for the progression of HFrEF remains unclear. González et al proposed that myocardial dysfunction and remodeling in patients with HFrEF were driven by the progressive loss of cardiomyocytes[22]. This loss of cardiomyocytes results from various modes of cell death, such as exaggerated autophagy, apoptosis, or necrosis, all of which are triggered by oxidative stress present within the cardiomyocytes because of ischemia, infection, or toxic agents. As the myocardium becomes more dysfunctional and develops abnormal metabolic needs, EAT satisfies its energy requirements. EAT exhibits a high lipolytic activity and might serve as a ready source of free fatty acids, leading to a decrease in EAT[23]. However, data regarding the correlation between LVEF and the amount of EAT are complicated and controversial. Some studies have reported the EAT volume measured by CT or echocardiography to be positively correlated with LVEF[12,13]. On the contrary, Doesch et al demonstrated a negative correlation between LVEF and EAT volume index, measured using CMR imaging[14]. This disagreement may reflect a difference in study population and the severity of HFrEF. In patients with HFrEF, RV systolic dysfunction is associated with impaired functional capacity and represents a more advanced stage[11]. However, RV function was not taken into account in previous EAT-related studies. Therefore, the current study considered RV function and observed that EAT volume index was positively correlated with RVEF (i.e., the worse the RV function was, the lower the EAT volumes were). A postmortem study by Schejbal showed that persistent RV failure was associated with thinning of the surrounding fatty layer[24]. At an early stage of HFrEF, preserved vascular distensibility maintains pulmonary vascular resistance within the normal ranges. However, as disease progresses, long-standing left atrial hypertension results in an increase in RV afterload, which intern leads to RV dysfunction[25]. Therefore, at a more advanced stage of HFrEF, the lipolytic activity of EAT increases with a diminished responsiveness to adjust to the

special energy demands of the heart, which may decrease EAT volumes.

On the contrary, several lines of evidence have suggested that an increase in EAT is significantly related to a proportional increase in LV mass[18]. A recent study by van Woerden et al revealed higher EAT volume in patients with HFpEF than in healthy controls[19]. Therefore, one can imagine that EAT is also involved in the pathophysiology of HFpEF. In patients with HFpEF, endothelial inflammation and oxidative stress induced by comorbidities, such as obesity, hypertension, diabetes mellitus, and chronic kidney disease, have recently been shown to drive myocardial dysfunction and remodeling[10]. In patients with visceral obesity, excessive fat cells tend to cause muscular hypertrophy and become dysfunctional due to surplus energy. Dysfunctional fat cells release pro-inflammatory adipokines into the bloodstream, possibly leading to chronic systemic inflammation associated with arterial stiffness, endothelial dysfunction in arterioles, and fibrosis, all of which have been implicated in the development of HFpEF[20,21]. Therefore, the new paradigm proposes that myocardial dysfunction and remodeling in HFpEF result from a series of bad flow caused by comorbidities, especially visceral obesity. This may explain a high EAT volume in patients with HFpEF although there was no significant difference in EAT volume between the HFpEF and control groups in the present study.

Recently, Pugliese et al showed the opposite association of EAT with cardiometabolic profile, haemodynamics and outcome in HF cohorts. In HFrEF, EAT accumulation is protective as a metabolic reservoir, therefore, EAT reduction is detrimental. In HFpEF, on the other hand, increased EAT plays an adverse role to promote haemodynamic derangements and alter adipogenesis by secretion of pro-inflammatory adipokines. Recent evidences suggest that natriuretic peptides activate lipolysis in adipose tissue in patients with HFrEF[24]. Consequently, increased BNP levels may contribute to the decrease in EAT in patients with HFrEF. A difference between the physiologic and pathophysiologic roles of EAT may reflect a difference in mechanisms responsible for the progression of cardiac dysfunction in patients with HFpEF and HFrEF. Such information on the difference in EAT volumes between the HFrEF and HFpEF groups may have a novel clinical implication in the therapy of HF. EAT may be a potential target for therapies using nutrient supply and drugs, such as glucagon peptide-like 1 analogs, sodium glucose transport 2 inhibitors, or ghrelin[26], to prevent the progression of HF. Further studies are needed to confirm the finding of this study.

This study has several limitations. First, due to the cross-sectional, retrospective nature of this study, we could not explore the direct causal relationships between EAT, comorbidities, and myocardial function and contractility. Therefore, it remains unclear whether EAT is a cause or a consequence of these diseases or merely an innocent bystander. Second, RV diastolic function was not taken into account in our study, although it may relate to EAT volume in patients with HF. Third, we did not measure various biological and metabolic markers such as pro-inflammatory adipokines and free fatty acids. Despite advances in the treatment of HF, our understanding of the energy metabolic mechanisms limiting cardiac pump function remains incomplete. In the future, the energy metabolism in the failing human heart needs to be elucidated. Finally, due to limited data in the HFpEF and control groups, only our primary question and not any additional questions could be answered.

In conclusion, this study demonstrated that HFrEF patients with RV dysfunction had less EAT compared to HFpEF patients, and less amount of EAT was related to the severity of RV dysfunction in HFrEF.

Acknowledgements

All authors have no COI to declare regarding the present study.

References

1. González N, Moreno-Villegas Z, González-Bris A, et al. Regulation of visceral and epicardial adipose tissue for preventing cardiovascular injuries associated to obesity and diabetes. Cardiovasc Diabetol 2017;16:44.
2. Iacobellis G, Ribaudo MC, Assael F, et al. Echocardiographic epicardial adipose tissue is related to anthropometric and clinical parameters of metabolic syndrome: a new indicator of cardiovascular risk. J Clin Endocrinol Metab 2003;88:5163-5168.
3. Pierdomenico SD, Pierdomenico AM, Cuccurullo F, et al. Meta-analysis of the relation of echocardiographic epicardial adipose tissue thickness and the metabolic syndrome. Am J Cardiol 2013;111:73-78.
4. Iacobellis G, Leonetti F. Epicardila adipose tissue and insulin resistance in obese subjects. J Clin Endocrinol Metab 2005;90:6300-6302.
5. Nakanishi K, Fukuda S, Tanaka A, et al. Peri-atrial epicardial adipose tissue is associated with new-onset nonvalvular atrial fibrillation. Circ J 2012;76:2748-2754.
6. Gaeta M, Bandera F, Tassinari F, et al. Is epicardial fat depot associated with atrial fibrillation? A systemic review and meta-analysis. Europace 2017;19:747-752.
7. Oka T, Yamamoto H, Ohashi N, et al. Association between epicardial adipose tissue volume and characteristics of non-calcified plaques assessed by coronary computed tomographic angiography. Int J Cardiol 2012;161:45-49.
8. Mancio J, Azevedo D, Saraiva F, et al. Epicardial adipose tissue volume assessed by computed tomography and coronary artery disease: a systematic review and meta-analysis. Eur Heart J Cardiovasc Imaging 2018;19:490-497.
9. Le Jemtel TH, Samson R, Ayinapudi K, et al. Epicardial adipose tissue and cardiovascular disease. Curr Hypertens Rep 2019;21:36.
10. Paulus WJ, Tschöpe C. A novel paradigm for heart failure with preserved ejection fraction: comorbidities drive myocardial dysfunction and remodeling through coronary microvascular endothelial inflammation. J Am Coll Cardiol 2013;62:263-271.
11. Merlo M, Gobbo M, Stolfo D, et al. The prognostic impact of the evolution of RV function in idiopathic DCM. JACC Cardiovasc Imaging 2016;9:1034-1042.
12. Khawaja T, Greer C, Chokshi A, et al. Epicardial fat volume in patients with left ventricular systolic dysfunction. Am J Cardiol 2011;108:397-401.
13. Tabakci MM, Durmuş Hİ, Avci A, et al. Relation of epicardial fat thickness to the severity of heart failure in patients with nonischemic dilated cardiomyopathy. Echocardiography 2015;32:740-748.
14. Doesch C, Haghi D, Flüchter S, et al. Epicardial adipose tissue in patients with heart failure. J Cardiovasc Magn Reson 2010;12:40.
15. Schulz-Menger J, Bluemke DA, Bremerich J, et al. Standardized image interpretation and post-processing in cardiovascular magnetic resonance - 2020 update: Society for Cardiovascular Magnetic Resonance (SCMR): Board of Trustees Task Force on Standardized Post Processing. J Cardiovasc Magn Reson 2020;22:19.
16. McKee PA, Castelli WP, McNamara PM, et al. The natural history of congestive heart failure: the Framingham study. N Engl J Med 1971;285:1441-1446.
17. Aschauer S, Kammerlander AA, Zotter-Tufaro C, et al. The right heart in heart failure with preserved ejection fraction: insights from cardiac magnetic resonance imaging and invasive haemodynamics. Eur J Heart Fail 2016;18:71-80.
18. Iacobellis G, Ribaudo MC, Zappaterreno A, et al. Relation between epicardial adipose tissue and left ventricular mass. Am J Cardiol 2004;94:1084-1087.
19. van Woerden G, Gorter TM, Westenbrink BD, et al. Epicardial fat in heart failure patients with mid-range and preserved ejection fraction. Eur J Heart Fail 2018;20:1559-1566.
20. Jelic S, Lederer DJ, Adams T, et al. Vascular inflammation in obesity and sleep apnea. Circulation 2010;121:1014-1021.
21. Taube A, Schlich R, Sell H, et al. Inflammation and metabolic dysfunction: links to cardiovascular diseases. Am J Physiol Heart Circ Physiol 2012;302:H2148-2165.
22. González A, Ravassa S, Beaumont J, et al. New targets to treat the structural remodeling of the myocardium. J Am Coll Cardiol 2011;58:1833-1843.
23. Iacobellis G, Corradi D, Sharma AM. Epicardial adipose tissue: anatomic, biomolecular and clinical relationships with the heart. Nat Clin Pract Cardiovasc Med 2005;2:536-543.

24. Schejbal V. Epicardial fatty tissue of the right ventricle — morphology, morphometry and functional significance. Pneumologie 1989;43:490-499.
25. Haddad F, Doyle R, Murphy DJ, et al. Right ventricular function in cardiovascular disease, part Ⅱ: pathophysiology, clinical importance, and management of right ventricular failure. Circulation 2008;117:1717-1731.
26. Nagaya N, Moriya J, Yasumura Y, et al. Effects of ghrelin administration on left ventricular function, exercise capacity, and muscle wasting in patients with chronic heart failure. Circulation 2004;110:3674-3679.