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Epicardial adipose tissue volume is an independent predictor of left ventricular reverse remodeling in patients with non-ischemic cardiomyopathy

Short title: Epicardial adipose tissue affects remodeling

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This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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Abbreviations:

AT, anaerobic threshold

BNP, brain natriuretic peptide

CMR, cardiovascular magnetic resonance imaging

CPX, cardiopulmonary exercise test

EAT, epicardial adipose tissue

HFimpEF, heart failure with improved ejection fraction

HFpEF, heart failure with preserved ejection fraction

HFrEF, heart failure with reduced ejection fraction

IMF, intramuscular fat

LVRr, left ventricular reverse remodeling

peak VO_2 , peak oxygen uptake

SFA, subcutaneous fat area

VE vs VCO_2 slope, minute ventilation versus carbon dioxide production slope

VFA, visceral fat area

Abstract

Background: In some patients with non-ischemic cardiomyopathy, left ventricular (LV) contraction is improved by optimal medical therapy, leading to LV reverse remodeling (RR). Patients with **heart failure with improved ejection fraction (HFimpEF)** and LVRR have a good prognosis, but the factors that predict RR are not fully understood. The relationship between body composition and cardiovascular disease has been reported. The present study aimed to assess the clinical predictors of LVRR in association with body composition.

Methods: We recruited patients who were diagnosed with non-ischemic cardiomyopathy between September 2017 and January 2020. Finally, 89 patients with a reduced LV ejection fraction (EF) (LVEF \leq 40%) were enrolled in this prospective study. Body composition, including ectopic fat, was measured in all patients using computed tomography. Echocardiography was performed 6 months after enrollment to evaluate LVRR.

Results: LVRR was observed in 39 patients (43.8%) after 6 months. In terms of the demographic findings, epicardial adipose tissue volume was greater in the LVRR group than in the non-LVRR group (135.2 cm³ [SD 128.4 cm³] vs. 88.9 cm³ [SD 54.6 cm³]; $p = 0.040$). The Kaplan–Meier analysis demonstrated that adverse cardiac events were significantly less frequent in the LVRR group than in the non-LVRR group (log-rank

test, $p = 0.013$). The multivariate logistic regression analysis identified epicardial adipose tissue volume as an independent predictor of LVRR (odds ratio [OR]: 1.010, 95% confidence interval [CI]: 1.001–1.01; $p = 0.036$).

Conclusion: Epicardial adipose tissue volume is an independent predictor of LVRR in patients with non-ischemic cardiomyopathy.

1. Introduction

Heart failure (HF) is a leading cause of death in many countries [1, 2]. It is caused by various factors, such as epicardial, myocardial, and endocardial disease; valvular disease; coronary artery disease; aortic disease; arrhythmia; and endocrine abnormalities. Because the treatment and evaluation methods for HF depend on left ventricular (LV) function, LV ejection fraction (EF) is used for classification and treatment selection in patients with HF. HF with preserved LVEF (typically considered as an LVEF of $\geq 50\%$) is defined as HFpEF, and HF with reduced LVEF (typically considered as an LVEF of $\leq 40\%$) is defined as HFrEF. Patients with an LVEF in the range of 41%–49% are defined as having HF with mid-range LVEF [3].

In some patients with non-ischemic cardiomyopathy, LV contraction is improved by optimal medical therapy (HF with improved EF [HFimpEF]). [4] These patients are known to have a better prognosis than patients in which LV contraction is not improved (HFrEF). [5-7] Predictors of LV reverse remodeling (RR) include younger age, presence of atrial fibrillation (AF), a smaller LV end-diastolic diameter (LVEDD), a higher LVEF at the first assessment [5], and diabetes mellitus [7].

The relationship between body composition and cardiovascular disease has also been reported. In a previous study, an increase in visceral fat area (VFA), but not

subcutaneous fat area (SFA), was associated with a decrease in LV strain in participants without overt cardiac disease [8]. Epicardial adipose tissue (EAT) volume was considered to be independently associated with coronary artery stenosis [9] and new-onset AF [10]. In addition, sarcopenia was associated with a poor prognosis in patients with HF [11]. We recently reported the importance of assessing intramuscular fat (IMF) in the thigh in addition to assessing muscle mass in patients with non-ischemic cardiomyopathy [12]. However, many aspects of the relationship between body composition and LVRR are still unclear. In the present study, we investigated the relationship between body composition, functional status, and LVRR.

2. Methods

2.1. Study Population

We recruited patients who were admitted for the first time to identify the cause of poor cardiac function between September 2017 and January 2020. Eligible patients were aged ≥ 18 years and poor cardiac function was diagnosed by echocardiography. Patients with ischemic cardiomyopathy diagnosed by cardiac catheterization were excluded. Other exclusion criteria were 1) LVEF $>40\%$; 2) severe valvular heart disease; 3) previous open heart surgery; 4) inherited myopathy; and 5) unwillingness to provide

informed consent. Finally, 97 patients with a reduced LVEF ($LVEF \leq 40\%$) were enrolled in this prospective study. Follow-up was conducted up to April 2021. The study protocol was approved by the institutional ethics committee of Osaka City University (approval number: 3785) and was conducted in accordance with the recommendations of the 1975 Declaration of Helsinki. Written informed consent was obtained from all patients.

2.2. Clinical Endpoints

To evaluate LVRR, we set the primary endpoint as cardiac function, which was evaluated by echocardiography 6 months after study enrollment. Patients were divided into two groups, as follows: (1) the LVRR group: LVEF of $>40\%$ and LVEF improved by ≥ 10 points from baseline to 6 months; (2) the non-LVRR group: LVEF of $\leq 40\%$ or LVEF not improved by ≥ 10 points throughout follow-up. Follow-up was performed by clinic visit, medical record review, and telephone contact with the patients or their physicians. The secondary endpoint was cardiovascular (CV) death or unexpected rehospitalization for cardiac events. Cardiac events were defined as worsening HF, implantation of cardiac resynchronization defibrillators, and fatal arrhythmia. The patients were followed up for a mean period of 17.3 months (SD 12.7 months).

2.3. Echocardiography

Echocardiography, including two-dimensional imaging, color Doppler imaging, and tissue Doppler imaging, was performed according to the current guidelines of the American Society of Echocardiography. [13] LVEF was defined by Simpson's modified method. Peak early (E), late (A) diastolic transmitral filling velocities, and deceleration time of E were measured. The early diastolic velocity of the medial mitral annulus (e') was measured using tissue Doppler imaging. Echocardiographic examinations of all patients were performed in a blinded manner by at least two experienced technicians.

2.4. Body Composition

Subcutaneous fat, ectopic fat, and skeletal muscle area were measured using computed tomography (CT) (Aquilion ONE™ 320-row detector dynamic volume CT scanner; Canon Medical Systems, Tokyo, Japan) within a few days before discharge in a clinically stable condition. EAT and IMF in the thigh were measured as ectopic fat. The slice thickness of EAT was 0.625 mm. The EAT volume was measured in the axial plane from the level of the pulmonary trunk bifurcation to the apex. The measurement position of the thigh was set between the middle part of the femoral head and the

midline of the patella. Volume analysis software (Synapse Vincent Version 4.4; Fujifilm Medical Systems, Tokyo, Japan) was used to identify adipose tissue based on a corresponding threshold attenuation value of -200 to -30 HU [14] [15]. The edges of the muscle groups were carefully traced using Synapse Vincent to calculate the cross-sectional area of the muscle groups and the subcutaneous adipose tissue (SAT) of the thigh. The thigh IMF area was defined as the fat interior to the thigh muscle. Muscle mass was calculated as follows: muscle mass = overall area of the thigh – (IMF + SAT + bone marrow area). In the thigh muscle, the percentage IMF (%IMF) was evaluated using the following formula: $\%IMF = (IMF \text{ area}) \div (IMF + \text{muscle area})$. CT images of the thigh were evaluated on both sides, and the average value was calculated. Image analysis was performed in a blinded manner.

2.5. Functional Status

Immediately before discharge, all patients underwent cardiopulmonary exercise testing (CPX) using an upright cycle ergometer (Strength Ergo 8; Fukuda Denshi, Tokyo, Japan) with a ramp protocol. Expired gas analysis was performed with the breath-by-breath method using an expired gas analyzer (Cpex-1; Inter Reha, Tokyo, Japan). The following parameters were measured and recorded before, during, and after CPX: peak

work rates, peak heart rate at exercise peak, anaerobic threshold (AT), peak oxygen consumption (VO_2), and minute ventilation (VE) vs. carbon dioxide production (VCO_2) slope. The AT was determined using the V-slope method [16]. We calculated the % predicted AT and peak VO_2 for comparison with a healthy cohort using data-based reference values [17].

Grip strength and lower-extremity muscle strength were measured on the same day as CPX. Grip strength was assessed using a handgrip dynamometer (Takei Physical Fitness Test Grip D; Takei Scientific Instruments Co. Ltd., Japan). As an index of lower-extremity muscle strength, the isometric knee extension muscle strength-to-weight ratio (kgf/kg) was calculated with the patient sitting in a chair. Strength measurements were performed using a hand-held dynamometer (JTech Commander PowerTrack II; JTech Medical, Salt Lake City, USA). In each case, two measurements were conducted on each of the left and right arms, and the highest measured value was recorded.

2.6. Clinical measurements

Baseline clinical parameters and laboratory data were collected from the patients' medical records. Data on medication were collected at discharge. Routine laboratory analyses were performed for all patients at discharge. Body mass index (BMI) was

computed as weight (kg) divided by the square of the height (m). Hypertension was defined as systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg, or treatment with antihypertensive agents before the onset of HF. Dyslipidemia was defined as fasting triglycerides ≥ 150 mg/dL, total cholesterol ≥ 220 mg/dL, low-density lipoprotein cholesterol ≥ 140 mg/dL, high-density lipoprotein cholesterol < 40 mg/dL, or treatment with lipid-lowering agents. Diabetes mellitus (DM) was defined based on the criteria of the Japan Diabetes Society (i.e., HbA1c $\geq 6.5\%$, fasting glucose ≥ 126 mg/dL, casual glucose ≥ 200 mg/dL, or treatment for diabetes). Smokers had smoked > 1 cigarette per day in the year prior to their exam. Serum brain natriuretic peptide (BNP), and troponin T levels were analyzed using certified methods. The estimated glomerular filtration rate (eGFR) was calculated using the modified IDMS–MDRD Study equation:
$$\text{eGFR (ml/min/1.73 m}^2\text{)} = 194 \times (\text{serum creatinine})^{-1.094} \times (\text{age})^{-0.287} \times (0.739 \text{ for women}).$$
 [18]

2.7. Statistical Analysis

Categorical variables are described as frequency (percentage). Continuous variables are described as mean with SD for normally distributed data and median [interquartile range] for non-normally distributed data. The normality of the data was evaluated using

the Shapiro–Wilk normality test. For comparisons between the LVRR group and the non-LVRR group, we used an unpaired t-test to compare normally distributed data, the Mann–Whitney U test for non-normally distributed data, and Fisher’s exact test for categorical variables. Spearman’s correlation coefficient between EAT and each continuous variable was calculated. Kaplan–Meier curves were constructed for the time to CV death or unexpected rehospitalization for cardiac events in the LVRR and non-LVRR groups, and the log-rank test was used for initial comparisons. Univariate and multivariate logistic regression analyses were performed to evaluate the prognostic factors for RR and an improvement in LVEF. The univariate analysis was performed with clinical variables, such as generally recognized parameters influencing HF, functional status, and body composition parameters. After the univariate analysis, among the candidate variables with p values of <0.10 , those thought to affect RR were entered using the forced entry method, and the multivariate analysis was performed. The results are expressed as odds ratios (ORs) and 95% confidence intervals (CIs). All statistical analyses were performed using JMP 13 (SAS Institute Inc., Cary, NC, USA). A *p* value of <0.05 was considered statistically significant.

3. Results

3.1. Patient Population

A study flowchart is shown in Supplementary Fig. 1. Ninety-seven patients with a reduced LVEF were enrolled in this prospective study. Two patients died and 6 patients withdrew within 6 months; thus, 89 patients were analyzed. The clinical characteristics of the LVRR and non-LVRR groups are shown in Table 1. Thirty-nine patients (43.8%) were allocated to the LVRR group, and 50 patients (56.2%) were allocated to the non-LVRR group. **There were no significant differences in age and sex.** Patients in the LVRR group tended to have higher resting diastolic and systolic blood pressures than those in the non-LVRR group, but no significant difference was observed in the presence of hypertension. **Similarly, there was no difference in oral medication use.** There was no significant difference in N-terminal brain natriuretic peptide or troponin concentration, but hemoglobin tended to be higher in the LVRR group. Echocardiographic findings also showed that the LV diameter tended to be shorter in the LVRR group, but there was no significant difference in LV contractility or left atrial diameter.

3.2. Functional Status and Body Composition Parameters

The results of body composition measurement and CPX data in the LVRR group and

non-LVRR group are shown in Table 2 and Supplementary Fig. 2. Strength indicators, including peak work rate in CPX, were significantly higher in the LVRR group. Muscle mass in the thigh, as measured by CT, was also significantly higher in the LVRR group. Focusing on fat, the SFA of the thigh was significantly larger in the LVRR group. For ectopic fat, there was no difference in %IMF in the thigh, but epicardial adipose tissue volume was significantly greater in the LVRR group (135.2 cm³ [SD 128.4 cm³] vs. 88.9 cm³ [54.6 cm³]; $p = 0.040$). As for the results of CPX before discharge, the VE vs. VCO₂ slope was significantly lower in the LVRR group (28.0 [SD 5.8] vs. 31.4 [SD 7.8]; $p = 0.027$), but there was no difference in the AT or peak VO₂.

3.3. Comparison of Echocardiography and CPX Data at 6 Months

We compared the results of echocardiography and CPX at 6 months between the LVRR group and the non-LVRR group (Supplementary Table 1). After 6 months, echocardiographic data showed that the LV and left atrial diameters were smaller, and contractility was improved in the LVRR group, and the CPX results showed that AT and peak VO₂ tended to improve in both the LVRR and non-LVRR groups, but there was no significant difference. The peak work rate was significantly higher in the LVRR group (90.9 W [SD 28.4 W] vs. 76.1 W [SD 18.8 W]; $p = 0.029$).

3.4. Association Between LVRR and Cardiac Events

The clinical endpoints were observed in 4 patients in the LVRR group and in 19 patients in the non-LVRR group. The Kaplan–Meier analysis results revealed that patients in the LVRR group had a lower risk of CV death or unexpected rehospitalization due to cardiac events than those in the non-LVRR group (log-rank test, $p = 0.013$; Fig. 1).

When the endpoint was set to CV death only, three events were noted. Because of the small number of events, it was not possible to prove a significant difference, but all three cases were observed in the non-LVRR group.

3.6. Predictive Variables for LVRR

The results of the univariate and multivariate logistic regression analyses are shown in Table 3. With the univariate analysis, resting systolic (OR: 1.029, 95% CI: 1.003–1.056; $p = 0.029$) and diastolic (OR: 1.044, 95% CI: 1.009–1.080; $p = 0.014$) blood pressure were significantly associated with LVRR. Although LVEF was not a predictor of LVRR in terms of echo indices, a smaller LVEDD and LV end-systolic diameter were better predictors of LVRR. As for the indices of muscle mass and strength, peak work rate on CPX, grip strength, and muscle area in the thigh were all predictors of LVRR. Because

muscle mass and strength are likely to be affected by sex, additional gender-specific analyses were conducted. All of these were significant predictors of LVRR in males, but none of them were predictors of LVRR in females (Supplementary Table 2). After the univariate analysis, the multivariate analysis was performed with exclusion of the variables that were susceptible to sex differences. The multivariate analysis, which was adjusted for age, diastolic blood pressure, serum N-terminal pro-brain natriuretic peptide concentration, and LVEDD, showed that EAT volume was an independent predictor of LVRR (OR: 1.010, 95% CI: 1.001–1.019; $p = 0.036$) (Table 3).

3.6. Correlation between EAT Volume and Other Findings

Supplementary Table 3 shows the correlation between EAT mass and other findings. EAT volume was positively correlated with BMI (Spearman's $r = 0.551$, $p < 0.001$), SFA in the thigh (Spearman's $r = 0.377$, $p < 0.001$), and muscle area in the thigh (Spearman's $r = 0.402$, $p < 0.001$). A positive correlation was also found between EAT and %IMF (Spearman's $r = 0.299$, $p = 0.003$). There was no correlation with serum N-terminal pro-brain natriuretic peptide concentration, cardiac function by echocardiography, or peak VO_2 , which suggests exercise tolerance. A comparison of the presence and absence of AF revealed that patients with AF tended to have more EAT,

although the difference was not significant (151.9 [SD 89.9] vs. 100.0 [SD 92.7]; $p = 0.072$).

4. Discussion

Our study demonstrated that EAT volume is an independent predictor of LVRR. A previous report demonstrated that EAT volume in patients with dilated cardiomyopathy is lower than in healthy controls [19]. However, to the best of our knowledge, this is the first report to demonstrate the apparent relationship between EAT volume and LVRR in patients with non-ischemic cardiomyopathy. Furthermore, what is unprecedented in this study is that CPX and muscle strength measurements were performed in all patients at the time of registration and 6 months later, and the relationship between physical function and RR was examined. In previous reports, it has been said that LVRR is observed in 10%–40% of patients with dilated cardiomyopathy [20, 21] or that two-thirds of patients diagnosed with HFpEF are actually HFimpEF [22]. Patients with HFimpEF demonstrate a good prognosis; thus, LVRR is important for appropriate treatment and prognosis prediction. Younger age, female sex, and AF are predictors of LVRR [5]. One report also showed that visceral fat associated with a decrease in LV strain in participants without overt cardiac disease [8]. We investigated the relationship

between body composition and LVRR in this study. The results showed that EAT volume was an independent predictor of LVRR.

In the present study, the LVRR group tended to have a higher BMI than the non-LVRR group. However, there was no association between LVRR and fat volume, such as %IMF, and muscle mass was significantly higher, suggesting that the difference in muscle mass affected BMI. In other words, BMI itself is not a predictor of LVRR, but the absence of sarcopenia is considered important. In the present study, muscle strength and muscle mass were predictors of LVRR in males. Sarcopenia is associated with a poor prognosis in patients with HF [23, 24], and maintenance of muscle mass may also contribute to LVRR.

Doesch et al. reported that EAT volume was lower in patients with dilated cardiomyopathy than in healthy subjects when measured by cardiac magnetic resonance imaging [19]. Tabakci et al. also reported the association between pericardial fat thickness and HF severity, which was investigated by echocardiography in patients with dilated cardiomyopathy. They found that the pericardial fat layer was thinnest in patients with New York Heart Association functional classification III/IV and inversely correlated with N-terminal pro-brain natriuretic peptide concentration [25]. Natriuretic peptides stimulate lipolysis by peptide infusion, both in isolated human fat cells and in

vivo [26, 27]. It has also been reported that the concentration of brain natriuretic peptide in pericardial fluid is higher than in blood [28]. These findings suggest that the concentration of natriuretic peptide in pericardial fluid increases in advanced HF, which may lead to degradation of EAT and a decrease in EAT volume.

A decrease in EAT volume in patients with reduced cardiac function means that HF is already at an advanced stage. As a result, LVRR may be less likely to occur. The evaluation of EAT volume is expected to improve prognosis by determining the severity of HF and enabling early therapeutic intervention in patients with non-ischemic cardiomyopathy. In the current study, it is unclear whether EAT itself contributes to the cardioprotective effect. To elucidate these mechanisms, it will be necessary to examine the relationship between EAT and myocardial pathological findings, as well as the relationship between various bioactive substances expressed in EAT and pathological conditions.

5. Study limitations

This study has several limitations that should be noted. First, as a prospective study conducted at a single center with a relatively small number of patients, the results may not apply to the general population. Second, we analyzed patients with non-ischemic

cardiomyopathy with a reduced LVEF, which might have included several different HF etiologies. In fact, 25% of these patients had dilated cardiomyopathy, while approximately 15% had AF. Third, scheduled catheter ablation was not included in the events during the 6-month follow-up. Although the prevalence of AF did not differ between the LVRR and non-LVRR groups, selection bias could not be fully denied. Therefore, large-scale investigations are required to assess the factors that predict LVRR.

6. Conclusion

In this study, epicardial adipose tissue volume was an independent predictor of LVRR in patients with non-ischemic cardiomyopathy.

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Table 1. Baseline characteristics of the patients with left ventricular reverse remodeling (LVRR) and non-LVRR.

	LVRR (n = 39)	Non-LVRR (n = 50)	<i>p</i> value
Male (%)	31 (79.5)	34 (68.0)	0.242
Age, years	56.6 ± 14.4	61.7 ± 13.3	0.087
NYHA class 1 (%)	13 (33.3)	10 (20.0)	0.222
BMI, kg/m ²	25.6 ± 6.0	22.1 ± 4.0	0.007
smoking history (%)	19 (48.7)	33 (66.0)	0.130
Concomitant disease			
Atrial fibrillation (%)	7 (18.0)	6 (12.0)	0.548
Hypertension (%)	23 (59.0)	23 (46.0)	0.286
Dyslipidemia (%)	11 (28.2)	15 (30.0)	1.000
Diabetes mellitus (%)	9 (23.1)	14 (28.0)	0.634
Vital signs			
Heart rate, bpm	71.6 ± 12.2	73.3 ± 14.8	0.573
Systolic blood pressure, mmHg	117.5 ± 18.5	108.9 ± 16.6	0.024
Diastolic blood pressure, mmHg	73.2 ± 14.8	65.8 ± 11.8	0.011
Treatments, n (%)			
ACE inhibitor or ARB	37 (94.9)	41 (82.0)	0.104
β-blocker	35 (89.7)	49 (98.0)	0.164
mineralocorticoid receptor antagonist	27 (69.2)	38 (76.0)	0.483
Loop diuretic	27 (69.2)	36 (72.0)	0.817
Laboratory data			
Hemoglobin, g/dL	14.7 ± 2.3	13.6 ± 2.2	0.028
Albumin, g/dL	3.9 ± 0.5	3.9 ± 0.5	0.875
Serum sodium, mEq/L	140.2 ± 2.4	139.5 ± 2.4	0.148
eGFR, ml/min/1.73m ²	60.3 ± 24.9	61.7 ± 29.3	0.812
High-sensitive troponin T, ng/mL	0.022 (0.011-0.031)	0.020 (0.012-0.034)	0.744
BNP, pg/mL	99.3 (57.0-234.6)	163.5 (85.0-467.7)	0.054
Baseline echocardiographic data			
LVEF, %	26.3 ± 6.4	24.1 ± 7.0	0.141
LVEDD, mm	59.1 ± 5.5	62.4 ± 7.0	0.017
LVESD, mm	49.7 ± 6.8	54.7 ± 8.2	0.003
LAD, mm	45.2 ± 7.6	42.2 ± 7.0	0.064

E, mm/sec	78.6 ± 21.5	80.7 ± 26.6	0.593
A, mm/sec	54.6 ± 23.5	66.4 ± 24.3	0.052
e', cm/sec	4.3 ± 1.4	4.5 ± 1.8	0.479
TRPG, mmHg	22.0 (14.0-35.3)	24.5 (18.8-35.0)	0.199

Values are mean ± standard deviation, median (inter-quartile range), or n (%).

NYHA, New York Heart Association; BMI, body mass index; ACE, angiotensin converting enzyme; ARB, angiotensin type 1 receptor blocker; eGFR, estimated glomerular filtration rate; BNP, B-type natriuretic peptide; LVEF, left ventricular ejection fraction; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; LAD, left atrial dimension; e', early diastolic velocity of the medial mitral annulus; TRPG, tricuspid regurgitation pressure gradient.

Table 2. Baseline functional status and body composition.

	LVRR (n = 39)	Non-LVRR (n = 50)	<i>p</i> value
Cardiopulmonary exercise test data			
Peak work rate, watts	89.6 ± 31.8	67.1 ± 21.9	<0.001
Anaerobic threshold, ml/min/kg	13.2 ± 2.5	12.7 ± 2.9	0.462
Anaerobic threshold %predicted, %	84.5 ± 18.2	83.4 ± 16.6	0.758
Peak oxygen uptake, ml/min/kg	19.5 ± 4.4	17.7 ± 5.2	0.104
Peak oxygen uptake %predicted, %	75.5 ± 17.9	73.5 ± 19.2	0.593
VE vs VCO ₂ slope	28.0 ± 5.8	31.4 ± 7.8	0.027
Muscle strength			
Mean grip strength, kg	29.6 ± 11.6	23.4 ± 12.4	0.018
Mean isometric knee extension strength, kgf/kg	288.9 ± 131.4	233.9 ± 128.0	0.050
Computed tomography scan			
Thigh subcutaneous fat area, cm ²	59.3 ± 33.6	46.1 ± 27.9	0.046
Thigh muscle area, cm ²	131.7 ± 38.6	107.6 ± 26.2	0.001
%Intramuscular fat area, %	3.1 ± 1.5	3.0 ± 1.6	0.620
Epicardial adipose tissue volume, cm ³	135.2 ± 128.4	88.9 ± 54.6	0.040

Values are mean ± standard deviation.

VE vs VCO₂ slope, ventilatory equivalent versus carbon dioxide output slope.

Table 3. Univariate and multivariate analysis for LVRR.

	Univariate analysis			Multivariate analysis		
	OR	95% CI	<i>p</i> value	OR	95% CI	<i>p</i> value
Age	0.973	0.943-1.004	0.090	0.972	0.933-1.012	0.171
BMI, kg/m ²	1.151	1.046-1.267	0.004			
Heart rate, bpm	0.991	0.961-1.022	0.569			
Systolic blood pressure, mmHg	1.029	1.003-1.056	0.029			
Diastolic blood pressure, mmHg	1.044	1.009-1.080	0.014	1.029	0.990-1.070	0.151
Atrial fibrillation	1.604	0.492-5.229	0.433			
Hypertension	1.688	0.724-3.934	0.226			
Hemoglobin, g/dL	1.239	1.020-1.505	0.031			
Albumin, g/dL	1.073	0.452-1.544	0.873			
eGFR, ml/min/1.73m ²	0.998	0.983-1.014	0.810			
High-sensitive troponin T, ng/L	0.993	0.976-1.010	0.432			
Log BNP	0.401	0.155-1.038	0.060	0.880	0.274-2.825	0.829
LVEF, %	1.049	0.984-1.117	0.142			
LVEDD, mm	0.919	0.854-0.988	0.022	0.911	0.836-0.993	0.035
LVESD, mm	0.917	0.863-0.974	0.005			
LAD, mm	1.059	0.996-1.127	0.068			
E, mm/sec	0.996	0.979-1.114	0.688			
A, mm/sec	0.979	0.957-1.001	0.058			
e', mm/sec	0.905	0.689-1.189	0.475			
Peak work rate, watts	1.035	1.014-1.057	0.001			
Anaerobic threshold, ml/min/kg	1.061	0.907-1.241	0.458			
Anaerobic threshold %predicted, %	1.004	0.979-1.029	0.754			
Peak oxygen uptake, ml/min/kg	1.077	0.984-1.180	0.108			
Peak oxygen uptake %predicted, %	1.006	0.983-1.031	0.589			
VE vs VCO ₂ slope	0.975	0.860-0.994	0.035			
Mean grip strength, kg	1.045	1.006-1.085	0.022			
Mean isometric knee extension strength, kgf/kg	1.003	1.000-1.007	0.054			
Thigh subcutaneous fat area, cm ²	1.014	1.000-1.029	0.050			
Thigh muscle area, cm ²	1.023	1.009-1.038	0.002			
%Intramuscular fat area, %	1.072	0.817-1.406	0.616			
Epicardial adipose tissue volume, cm ³	1.008	1.000-1.015	0.034	1.010	1.001-1.019	0.036

Abbreviations as in Table 1 and 2. OR, odds ratio; CI, confidence interval.

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Figure captions:

Figure 1. Kaplan-Meier estimates of risk of cardiac events.

The patients with LVRR group had a lower risk of cardiovascular death or unexpected rehospitalization for cardiac events than Non-LVRR group (log-rank test $p = 0.0128$).

LVRR (left ventricular reverse remodeling): left ventricular ejection fraction (LVEF) $\leq 40\%$ at baseline and $> 40\%$ and ejection fraction (EF) improved $\geq 10\%$ at 6months. Non-LVRR: LVEF $\leq 40\%$ throughout follow-up.

Figure S1. Study population.

EF, ejection fraction; LVEF, left ventricular ejection fraction

LVRR (left ventricular reverse remodeling): LVEF $\leq 40\%$ at baseline and $> 40\%$ and EF improved $\geq 10\%$ at 6months. Non-LVRR: LVEF $\leq 40\%$ throughout follow-up.

Figure S2. Comparison of body composition parameters in the LVRR group and the Non-LVRR group.

The subcutaneous fat area and muscle mass in the thigh was significantly higher in the LVRR group. There was no difference in intramuscular fat area in the thigh, but epicardial adipose tissue volume was significantly greater in the LVRR group.