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Clinical Trials Study

Epicardial adipose tissue in obesity with heart failure with preserved ejection fraction：cardiovascular magnetic resonance biomarker study

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Abstract

BACKGROUND

+ADw-html+AD4APA-p+AD4-Obesity has become a serious public health issue, significantly elevating the risk of various complications. It is a well-established contributor to Heart failure with preserved ejection fraction (HFpEF). Evaluating HFpEF in obesity is crucial. Epicardial adipose tissue (EAT) has emerged as a valuable tool for validating prognostic biomarkers and guiding treatment targets. Hence, assessing EAT is of paramount importance. Cardiovascular magnetic resonance (CMR) imaging is acknowledged as the gold standard for analyzing cardiac function and morphology. We hope to use CMR to assess EAT as a bioimaging marker to evaluate HFpEF in obese patients.+ADw-/p+AD4APA-/html+AD4-

AIM

To assess the diagnostic utility of cardiovascular magnetic resonance (CMR) for evaluating heart failure with preserved ejection fraction (HFpEF; left ventricular (LV) ejection fraction ≥ 50%) by measuring the epicardial adipose tissue (EAT) volumes and EAT mass in obese patients.

METHODS

Sixty-two obese patients were divided into two groups for a case-control study based on whether or not they had heart failure with HFpEF. The two groups were defined as HFpEF+ and HFpEF-. LV geometry, global systolic function, EAT volumes and EAT mass of all subjects were obtained using cine MR sequences.

RESULTS

Forty-five patients of HFpEF- group and seventeen patients of HFpEF+ group were included. LV mass index (g/m^2) of HFpEF+ group was higher than HFpEF- group ($P < 0.05$). In HFpEF+ group, EAT volumes, EAT volume index, EAT mass, EAT mass index and the ratio of EAT/(left atrial (LA) left-right (LR) diameter) were higher compared to HFpEF- group ($P < 0.05$). In multivariate analysis, Higher EAT/LA LR diameter ratio was associated with higher odds ratio of HFpEF.

CONCLUSION

EAT/LA LR diameter ratio is highly associated with HFpEF in obese patients. It is plausible that there may be utility in CMR for assessing obese patients for HFpEF using EAT/LA LR diameter ratio as a diagnostic biomarker. Further prospective studies, are needed to validate these proof-of-concept findings.

INTRODUCTION

Obesity has become a serious public health issue, significantly elevating the risk of various complications, including heart disease, type 2 diabetes, and hypertension [1]. It is a well-established contributor to heart failure (HF) [2]. Heart failure with preserved ejection fraction (HFpEF) is a prevalent and deadly clinical syndrome characterized by HF with a left ventricular ejection fraction (LVEF) $\geq 50\%$. Within the broader HFpEF population, the obesity-HFpEF phenotype has been identified as a distinct subset, potentially necessitating specific treatments [3]. Recently, there is growing recognition of the importance of anti-atherogenic and anti-inflammatory effects, known as 'metainflammatory' mechanisms, in the treatment of "obese HFpEF" [4]. Therefore, evaluating HFpEF in obesity is crucial.

Epicardial adipose tissue (EAT) refers to the fat surrounding the heart in the epicardium, also known as visceral fat [5]. Studies have linked EAT with HF, revealing higher EAT volume in HF patients with HFpEF [6-7]. Consequently, EAT has emerged as a valuable tool for validating prognostic biomarkers and guiding treatment targets [8-9]. Hence, assessing EAT is of paramount importance.

Accurate detection and quantification of EAT can be accomplished through 2-dimensional (2D) echocardiography, contrast-free computed tomography (CT), and magnetic resonance imaging (MRI) [10]. Echocardiography, a widely used cardiac imaging method for EAT measurement, does not expose patients to ionizing radiation [11-12]. However, it predominantly provides 2D cardiac images, measuring only the thickness, not the volume or mass of EAT [13]. Additionally, echocardiography-derived measurements may be more prone to inter-observer errors compared to cross-sectional modalities. Consequently, echocardiography is only accurate for measuring the maximum EAT thickness [14]. Nevertheless, the definitive EAT thickness threshold for use as a prognostic biomarker is yet to be determined [15]. Moreover, the applicability of EAT thickness is often constrained by suboptimal acoustic windows in obese patients.

More recently, the heightened EAT in patients exhibiting the HFpEF phenotype can be assessed through CT, potentially indicating adverse cardiac function [16]. Evaluation of cardiac function is feasible. However, CT is constrained by radiation exposure. Cardiovascular magnetic resonance (CMR) imaging is acknowledged as the gold standard for analyzing cardiac function and morphology [17]. Utilizing three-dimensional (3D) cine images, CMR enables accurate and reproducible quantification of EAT thickness, volume, and mass. Some recent CMR studies have compared EAT quantities in HFpEF groups with controls, emphasizing the need to focus on EAT beyond an individual's overall body fat concerning HFpEF [18-19]. However, it is conceivable that obesity could confound such findings due to the general increase in adipose tissue throughout the body. To our knowledge, no studies have investigated

EAT metrics (including volume or mass) in obese patients using CMR to determine the association with HFpEF and whether EAT metrics could serve as a biomarker for predicting HFpEF in the obese population. Therefore, this study aims to employ CMR to examine EAT in the obese population with and without HFpEF, considering the association with co-morbidities, biomarkers, contractility parameters, and myocardial function assessed by CMR.

MATERIALS AND METHODS

Study participants

The study followed a case-control, prospective clinical design, enrolling 69 obese individuals from October 2019 to August 2020 at Shanghai Jiao Tong University School of Medicine Affiliated Renji Hospital. HFpEF patients meeting specific criteria were included: (1) Left ventricular (LV) ejection fraction (LVEF) ≥ 50%, assessed by echocardiography; (2) New York Heart Association (NYHA) class ≥ II, with either E/e' > 13 and mean e'septal and lateral wall < 9 cm/s on echocardiography; (3) plasma brain natriuretic peptide (BNP) > 35 pg/mL [20]. Exclusion criteria were: (1) general contraindication to CMR; (2) poor imaging quality; (3) heart failure with mid- range ejection fraction (HFmrEF) and heart failure with reduced ejection fraction (HFrEF); (4) congenital heart disease; (5) acute ischemic cardiac injury; (6) hypertrophic cardiomyopathy; (7) greater than moderate valvular disease; (8) sarcoidosis; (9) amyloidosis; (10) thalassemia; (11) hemochromatosis. The study complied with the 1964 Declaration of Helsinki and subsequent amendments.

Five patients were excluded due to exclusion criteria, and 2 were excluded for poor image quality and MRI contraindications. Seventeen obese patients with HFpEF and 45 obese patients without HFpEF, meeting inclusion criteria with matched gender and age, were recruited. Obesity was defined as a body mass index (BMI) ≥ 30.0 kg/m^2, following Asian-Pacific cutoff points [21]. All participants provided written, informed consent. BMI (kg/m^2) was calculated, and measurements included blood pressure, serum cholesterol, serum triglycerides, serum high-density lipoprotein cholesterol

(HDL), and serum low-density lipoprotein cholesterol (LDL). Fasting glucose and hemoglobin A1c (HbA1c) levels were also assessed. The study flow diagram is depicted in Figure 1.

MR protocol

All examination data were obtained using a 3.0 Tesla MR scanner (Prisma, Siemens, Erlangen, Germany) equipped with a 32-channel cardiac coil. Cine imaging was acquired through retrospective ECG gating with balanced steady-state free-precession during horizontal and vertical long-axis views, and in 16 short-axis slices covering the entire left ventricle to evaluate left ventricular function and cardiac mechanics. Data in the short-axis plane were collected at the mid-ventricular level. Imaging parameters comprised a repetition time (TR) of 326.6 ms, echo time (TE) of 1.09 ms, flip angle (FA) of 35°, field of view (FOV) of 385×385 mm^2, matrix of 156×192, slice thickness of 8 mm, slice gap of 4 mm, receiver bandwidth (BW) of 1085 Hz/px, GRAPPA acceleration factor 2, linear phase-encoding ordering, and 25 cardiac phases.

Data analysis

EAT was defined as the fat between the myocardium and the visceral pericardium. The borders of the EAT image were manually delineated on contiguous end-diastolic short-axis slices from the base to the apex using commercially available software (cvi42, Circle Cardiovascular Imaging Inc., Calgary, Canada) (Figure 2). Additionally, LV endocardial and epicardial borders were manually outlined slice by slice based on the initial contour set at end-diastole. EAT mass was estimated by multiplying the EAT volume by 0.92 [22]. CMR image analyses were independently conducted by two experienced radiologists who were blinded to the study. LV end-diastolic volume (LVEDV), LV end-systolic volume (LVESV), and LV mass (LVM) were measured and normalized to body surface area. LV stroke volume (LVSV) was calculated by subtracting LVESV from LVEDV. Left ventricular ejection fraction (LVEF) was computed as LVSV/LVEDV×100%. The measurement of left atrial anterior-posterior

(LA AP) diameter and left atrial left-right (LA LR) diameter followed a previously reported method [23].

Statistical analysis

The normality of continuous samples was assessed using the Kolmogorov-Smirnov test for normal distribution. Group comparisons were conducted using Student's t-test for continuous variables or Fisher's exact test for categorical variables. Initial univariate analyses and stepwise multivariate linear regression analyses were executed to identify predictors of the odds of HFpEF in the obese population. Covariates with a univariate P value < 0.10 were included in the multivariate logistic regression analysis [24-25]. Pearson's correlation coefficient was employed for correlation analyses. A P value < 0.05 was considered significant. Intra- and inter-observer repeatability of parameters derived from CMR were assessed using the intra-class correlation coefficient (ICC) in 30 randomly selected patients from the same cohort [26]. An ICC > 0.75 was considered indicative of good agreement [27]. Descriptive and comparative statistical analyses were carried out using SPSS version 23.0 (IBM Corp., Armonk, United States) and GraphPad Prism v. 8.0 (GraphPad Software, Inc., CA, United States).

RESULTS

Baseline characteristics

Table 1 summarizes the baseline characteristics. The mean ages of the obese populations with HFpEF (HFpEF+) and without HFpEF (HFpEF-) were 42.94 ± 3.37 years and 36.60 ± 1.80 years, respectively ($P > 0.05$). In the HFpEF+ group, 17.6% were older than 60 years, compared to 0.02% in the HFpEF- group. Among HFpEF+ patients, 64.7% were males, while 55.6% of HFpEF- patients were males. No significant differences were observed in body surface area (BSA), body mass index (BMI), brain natriuretic peptide (BNP), and resting diastolic blood pressure (DBP), but there were significant differences between the two groups ($P < 0.05$). The prevalence of fatty liver was higher in the HFpEF- group (58.8%) compared to the HFpEF+ group (28.9%) ($P =$

0.0253), with no significant differences in other complications. Resting systolic blood pressure (SBP), regardless of medication control, was significantly higher in HFpEF+ patients than in the HFpEF- group (P = 0.0370).

CMR parameters of left ventricular morphology and function epicardial adipose tissue of the obesity in populations with and without HFpEF

The measurements' results are detailed in Table 2. In terms of morphological characteristics, the HFpEF+ group displayed significant remodeling with a greater LV mass index compared to the HFpEF- group. No significant differences were observed in other morphological and functional parameters between the two groups. Regarding epicardial adipose tissue, both EAT volume and EAT mass were significantly larger in HFpEF+ individuals, and these differences persisted after adjustment for BSA (P = 0.04 for EAT volume / BSA and P = 0.04 for EAT mass / BSA). A significant difference in the EAT/LA LR diameter ratio was observed between the two groups (P = 0.02) (Figure 3).

Associations of epicardial adipose tissue and morphological and functional parameters in HFpEF+ group

The correlation analysis results of all four epicardial adipose tissue parameters (EAT volume, EATi, EAT mass, EAT mass index) with eight CMR-measured LV morphological and functional parameters are presented in Table 3. No significant correlations were observed.

Logistic Regression Analysis

In univariate logistic regression analysis, EAT mass index (odds ratio [OR] = 1.05, P = 0.04, 95%CI: 1.00-1.10), EATi (OR = 1.05, P = 0.04, 95%CI: 1.00-1.09), and EAT/LA LR diameter ratio (OR = 3.99, P = 0.03, 95%CI: 1.17-13.58) showed significant associations with HFpEF. EAT volume (OR = 1.02, P = 0.051, 95%CI: 1.00-1.04) trended toward an association with HFpEF. In multivariate analysis, the variable associated with HFpEF in the obese population was the EAT/LA LR diameter ratio (OR = 4.60, *P* = 0.02, 95%CI: 1.22-17.35) (Table 4).

Intraobserver and interobserver variability

Table 5 summarizes the ICC values for both intraobserver and interobserver reproducibility. The eight CMR-measured parameters demonstrated high reproducibility, ranging from 0.71 to 0.93 for intra-observer and 0.88 to 0.98 for inter-observer, respectively.

DISCUSSION

In this study, we conducted a comprehensive comparison of EAT volume, mass, and functional characteristics, as determined by CMR, among individuals with obesity in the absence of HFpEF (HFpEF-) and HFpEF+ groups. The main findings of our study are as follows: 1) EAT volume and EAT mass were significantly increased in the obese HFpEF+ group compared to the obese HFpEF- group, and these differences persisted after adjustment for body surface area (BSA), 2) in the obese population, the EAT/LA LR diameter ratio can serve as an alternative method to differentiate between HFpEF+ and HFpEF- groups, and 3) a higher EAT/LA LR diameter ratio was associated with a higher risk of HFpEF after adjusting for potential confounders.

The utilization of CMR for EAT measurement in our study provides a comprehensive assessment of cardiac structure and function in individuals with HFpEF [28]. Additionally, our study contributes to the existing literature by implementing and evaluating the quantification of EAT using MRI during diastole [29]. In a prior study, we demonstrated CMR's sensitivity and accuracy in detecting conventional atrial geometry in dialysis patients with HFpEF [30]. The present study, employing CMR to measure EAT, holds significant strengths over prior investigations examining the association between EAT and HFpEF in an obese population.

Our findings revealed that EAT volume and EAT mass, determined by CMR, were significantly higher in the HFpEF+ group compared to the HFpEF- group, with significant differences in EATi and EAT mass index as well. EAT, recognized as a risk factor for heart failure, particularly in the obese population [30,32], is implicated as an independent risk factor for HFpEF [33-34]. EAT's invasion into and around coronary arteries contributes to microvascular dysfunction, ventricular dilatation, and heart failure [12]. Adipocytes within EAT possess endocrine functions, synthesizing aldosterone and angiotensinogen [35]. Moreover, EAT serves as a marker for inflammatory factors [36]. Consistent with previous echocardiographic studies associating EAT thickness with HFpEF [37], our results further support this relationship.

In our study, there was a significant increase in LV mass index in the HFpEF+ group compared to the HFpEF- group. The space between the myocardial surface and the visceral pericardium may be filled with EAT, potentially covering the entire epicardium [38]. In the obese population, the excess EAT could impose an increased burden on both ventricles, ultimately leading to left ventricular hypertrophy [39]. These findings are consistent with prior investigations into obesity. A previous study utilizing CMR demonstrated that individuals with uncomplicated obesity and HFpEF exhibited extensive LV geometric remodeling, impaired ventricular function, and increased myocardial thickness [40].

Our research revealed that the EAT/LA LR diameter ratio was higher in the HFpEF+ group compared to the HFpEF- group, and this ratio was significantly associated with HFpEF. While no prior study has specifically investigated changes in the EAT/LA LR diameter ratio, it has been demonstrated to be impaired before left atrial enlargement in obese patients with HFpEF experiencing diastolic heart failure [41]. A recent study utilizing transthoracic echocardiography indicated that increased EAT thickness was linked to poorer left atrial function in HFpEF [42]. Additionally, another echocardiography-related study suggested that the presence of increased EAT is associated with a greater increase in cardiac filling pressures in patients with the obese phenotype of HFpEF [11]. Thus, the utilization of EAT/LA LR, assessed through CMR, could play a crucial role in the differentiation and diagnosis of obese HFpEF in clinical practice in the future. The EAT/LA LR diameter ratio may serve as a novel imaging biomarker.

Our study demonstrated no correlation between the four epicardial adipose tissue parameters (EAT volume, EATi, EAT mass, EAT mass index) and CMR-measured LV morphological and functional parameters. This finding aligns with some of the current studies [43]. It is plausible that our sample size is relatively small, and more conclusive results may emerge in the future with a larger sample size.

According to prior studies, age significantly contributes to EAT accumulation and may exert a substantial influence on its buildup [44]. In our study, there was no significant difference in age between the two groups, indicating that the effect of age on EAT was excluded. Despite the lack of statistical significance, there appears to be a trend towards older age in patients with HFpEF, supported by a higher proportion of subjects aged over 60 years in the HFpEF+ cohort. Additionally, resting SBP was significantly higher in HFpEF+ patients than in the HFpEF- group. Patients with HFpEF exhibit reduced aortic distensibility and increased systolic blood pressure [45]. Previous findings suggest that obesity has a detrimental impact on prehypertension and hypertension, irrespective of general obesity or abdominal obesity presence [46].

CONCLUSION

EAT/LA LR diameter ratio is highly associated with HFpEF in obese patients. It is plausible that there may be utility in CMR for assessing obese patients for HFpEF using EAT/LA LR diameter ratio as a diagnostic biomarker. Further prospective studies, are needed to validate these proof-of-concept findings.

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