



# Extent of coronary atherosclerosis is associated with deterioration of left ventricular global longitudinal strain in patients with preserved ejection fraction undergoing coronary computed tomography angiography

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## ABSTRACT

**Background:** This study aimed to investigate the association between the extent and severity of coronary atherosclerosis, epicardial adipose tissue (EAT) accumulation, and left ventricular (LV) global longitudinal strain (GLS) in patients with preserved LV ejection fraction (LVEF) and without LV regional wall motion abnormalities. **Methods:** This study included 169 preserved LVEF patients without LV wall motion abnormalities who underwent coronary computed tomography (CT) angiography for the assessment of suspected coronary artery disease (CAD). The segment stenosis score (SSS) and segment involvement score (SIS) were calculated to evaluate CAD extent. The EAT volume was defined as CT attenuation values ranging from  $-250$  to  $-30$  HU within the pericardial sac. LVGLS was measured using echocardiography to assess subclinical LV dysfunction.

**Results:** All patients had preserved LVEF of  $\geq 50\%$ , and the mean LVGLS was  $-18.7\%$  ( $-20.5\%$  to  $-16.9\%$ ). Mean SSS and SIS were 2.0 (0–5) and 4.0 (0–36), respectively, while mean EAT volume was 116.1 mL (22.9–282.5 mL). Multivariate analysis using linear regression model demonstrated that LVEF ( $\beta$ ,  $-17.0$ ; 95% CI,  $-20.9$  –  $-13.1$ ), LV mass index ( $\beta$ , 0.03; 95% CI, 0.01–0.06), and EAT volume ( $\beta$ , 0.010; 95% CI, 0.0020–0.0195) were independently associated with LVGLS; however, obstructive CAD was not. The multivariate models demonstrated that SSS ( $\hat{\beta}$ , 0.12; 95% CI, 0.05–0.18) and SIS ( $\hat{\beta}$ , 0.27; 95% CI, 0.10–0.44) were correlated with deterioration of LVGLS, independent of other parameters.

**Conclusion:** This study demonstrates that EAT volume and CAD extent are associated with the deterioration of LVGLS in this population.

## 1. Introduction

Coronary artery disease (CAD) is a progressive disease that contributes to the development of acute coronary syndrome (ACS) and heart failure [1]. CAD is the most common cause of heart failure, both with preserved and reduced ejection fractions, in the US adult population [2–4]. The importance of coronary atherosclerosis in relevant underlying conditions, such as left ventricular (LV) dysfunction, is increasingly being recognized [5,6]. CAD is a risk factor for incident heart failure

with preserved ejection fraction (HFpEF) after adjusting for common cardiovascular comorbidities, and this risk is partially explained by left ventricular diastolic dysfunction [7]. Left ventricular global longitudinal strain (LVGLS), assessed using echocardiography, is a sensitive marker of subclinical LV dysfunction which precedes the deterioration of LV function and heart failure [8,9]. Furthermore, the presence of regional asynergy can cause deterioration of the LVGLS, which also allows the assessment of LV wall motion abnormalities [10]. Nevertheless, there is limited knowledge on the relationship between CAD extent and severity

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and subclinical LV dysfunction in preserved LVEF patients without LV wall motion abnormalities (see Fig. 1).

Coronary computed tomography angiography (CCTA) is widely used in clinical practice as a first-line test for symptomatic or asymptomatic patients at risk of obstructive CAD, allowing noninvasive assessment of CAD severity and extent [11]. In addition, CCTA enables the quantification of epicardial adipose tissue (EAT) volume, which is closely related to the development of CAD, atrial fibrillation, and heart failure, with or without preserved LV ejection fraction (LVEF) [12–16]. Recent clinical studies have demonstrated that EAT volume is associated with CAD severity and coronary microvascular dysfunction (CMD) [17]. These findings suggest that the EAT may play a pivotal role in the development of subclinical LV dysfunction in patients with CAD. In this CCTA study, we aimed to investigate the association between structural features, including CAD severity and extent, and EAT volume with LVGLS in patients with preserved LVEF without LV wall motion abnormalities.

## 2. Methods

### 2.1. Study population

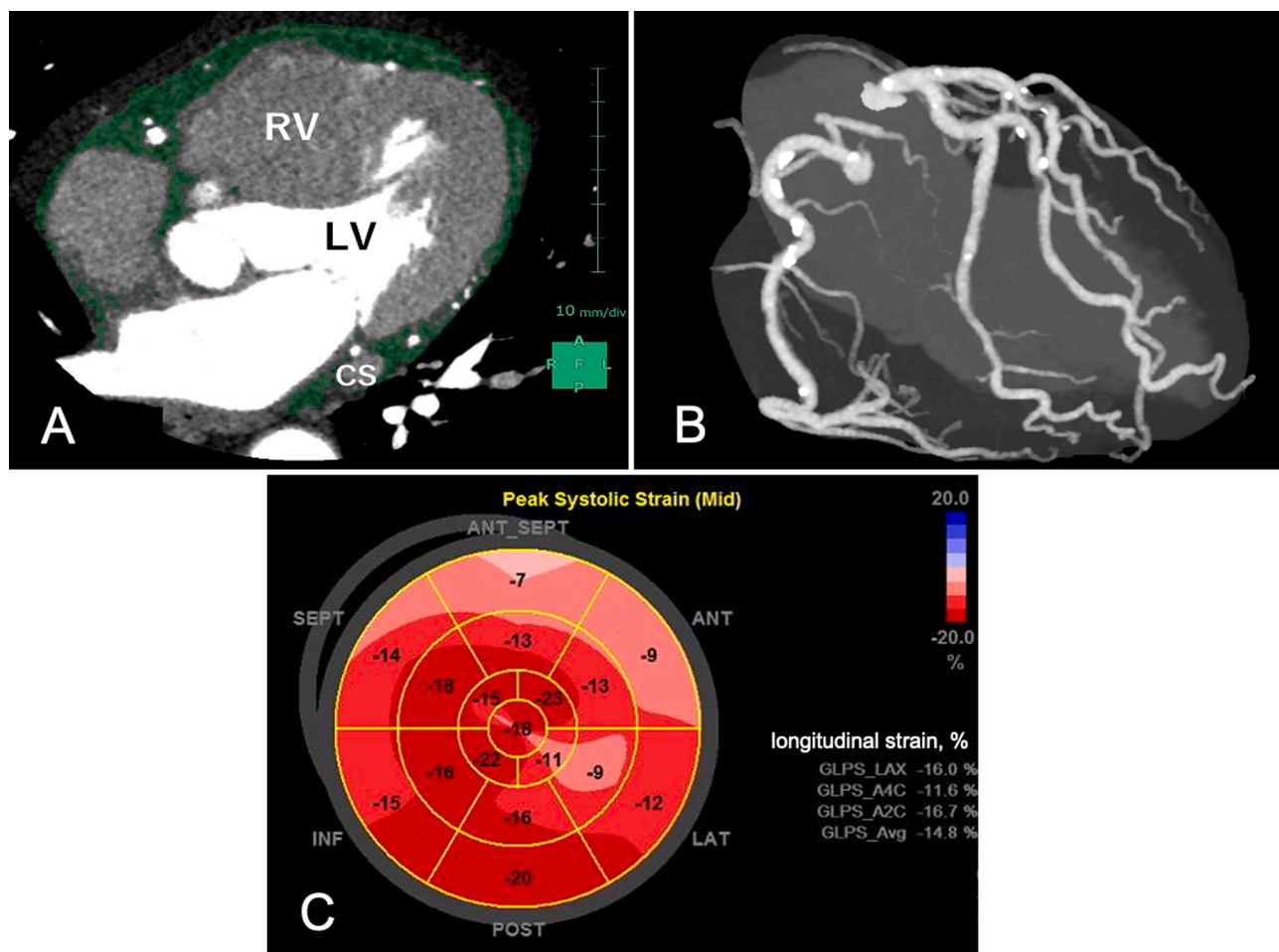
The ethics committee of Kashibaseiki Hospital approved the study protocol (2021-F), and each patient provided written informed consent before the CCTA examination, which was conducted in compliance with the protocol and the Declaration of Helsinki. This study was a

retrospective analysis from our database, consisting of patients with suspected CAD who underwent CCTA examination between April 2017 and December 2019. We identified consecutive symptomatic patients who underwent CCTA and two-dimensional transthoracic Doppler echocardiography (TTDE) (n = 402). The exclusion criteria for this study were as follows: (1) ACS (n = 19), (2) previous history of myocardial infarction (n = 10) or coronary revascularization (n = 79), (3) LVEF < 50% or abnormal LV wall motion abnormality (n = 105), (4) atrial fibrillation (n = 15), and (5) poor image quality (n = 5). The final study population included 169 patients with preserved LVEF but without focal LV wall motion abnormalities or known CAD.

### 2.2. Echocardiography and global longitudinal strain

TTDE examination was performed before CCTA examination in all study patients. All TTDE examinations were performed in a standard manner by experienced cardiac echo sonographers using the Vivid S70 (General Electric, Milwaukee, WI, USA) under continuous ECG monitoring [18]. LVEF was calculated using apical 2-chamber and 4-chamber views. Mitral inflow was assessed using pulse-wave Doppler to measure the early (E) and late (A) peak velocities. Early diastolic mitral annular velocity (e') was also measured using tissue Doppler imaging in the septal wall, providing the ratio of E to e' (E/e').

Measurements of the longitudinal strain at the peak systolic phase were obtained using grayscale images recorded in the apical 4-chamber, 2-chamber, and long-axis views. The LVGLS was analyzed offline using a



**Fig. 1. A representative case of increased EAT volume with coronary atherosclerosis and impaired LVGLS.** A 61-year male with obstructive CAD and increased EAT volume (A) and CAD extent (B) showing impaired LVGLS (C). (A) EAT volume, 194 mL; (B) nonobstructive CAD with a CACS of 440.6 Agatston units; (C) impaired LVGLS, -14.8%; LVGLS was calculated by averaging the negative peak strain from 18 ventricular segments from the apical 4-chamber, 2-chamber, and long-axis views.

dedicated software. For the accurate evaluation of LVGLS, sonographers ensured that TTDE images clearly detected the endocardial border throughout the cardiac cycle. The LV endocardial border was manually traced, and the software algorithm automatically divided the LV apical view into six segments for speckle tracking throughout the cardiac cycle. The LVGLS was obtained by averaging all segmental strain values from the apical 4-chamber, 2-chamber, and long-axis views [9]. All echocardiographic measurements were performed based on the recommendations of the American Society of Echocardiography by two independent cardiologists (Y.K. and K.H.) who were blinded to the patient demographics or CCTA results.

### 2.3. CCTA image acquisition and analysis

All CCTA examinations were performed using 320-row multidetector computed tomography (Aquilion ONE/NATURE Edition; Canon Medical Systems, Inc., Japan) [19]. The scan parameters were detector collimation of  $0.5 \times 320$  mm, gantry rotation time of 0.35 sec, tube voltage of 120 kV, and tube current of 130–600 mA. An electrocardiogram-triggered prospective gating method was used for CCTA imaging.

The Agatston method was used to assess coronary artery calcium score (CACS) at a fixed thickness of 3 mm [20]. A bolus tracking method was used for image acquisition, in which a nonionic contrast medium of 270 mg I/kg was administered using a power injector. A region of interest (ROI) was placed in the ascending aorta at the bronchial bifurcation level. When the computed tomography (CT) value of the ROI exceeded 150 Hounsfield units (HU), ECG-synchronized scans were performed within a single breath-hold. Images were reconstructed for coronary artery analysis with a cross-sectional thickness of 0.5 mm and reconstruction increment of 0.25 mm.

All CCTA image analyses were performed using a dedicated software (VINCENT, Fujifilm Inc., Tokyo, Japan). CACS was categorized into four categories as follows: 0, 1–99, 100–399, and >400 Agatston units [21]. Coronary luminal stenosis was reported based on a 16-segment AHA model by 2 observers (K.O. and H.I.). To evaluate the extent and severity of CAD, segment stenosis score (SSS) and segment involvement score (SIS) were calculated [20]. Briefly, using 16 segments, we measured the percentage of luminal stenosis in images with plaques on CPR short-axis images and classified luminal stenosis as grade 1 to grade 5. The SIS score ranged from 0 to 16 points, whereas the SSS ranged from 0 to 80 points. Obstructive CAD was defined as the presence of coronary plaques with  $\geq 50\%$  luminal stenosis of one or more major epicardial vessels and/or  $\geq 50\%$  luminal stenosis of the left main coronary segment. Non-obstructive CAD was defined as patients with  $< 50\%$  luminal stenosis of the epicardial coronary arteries. Otherwise, the patients were categorized as not having CAD.

### 2.4. EAT volume measurement

EAT volume was measured from contrast-enhanced CT images using Synapse Vincent software (Fujifilm Inc.) [19]. To measure EAT volume, we extracted multiple equidistant axial planes according to the size of each heart. The upper limit of the slice was at the bifurcation of the pulmonary artery trunk and the lower slice contained any structure of the heart. In each plane, the software automatically detected a smooth, closed pericardial contour as the region of interest, where the software automatically identified adipose tissue with CT attenuation values ranging from  $-250$  to  $-30$  HU within the pericardial sac. The EAT volume was calculated as the sum of the EAT areas.

### 2.5. Statistical analysis

Statistical analysis was performed using R software package (version 3.2.1; R Foundation for Statistical Computing, Vienna, Austria). Categorical variables were reported as counts (percentage), and continuous variables were reported as mean (SD) or median (interquartile range,

IQR). Statistical significance was assessed using the chi-square test, Fisher's exact test, Student's *t*-test, Kruskal-Wallis test, or Mann-Whitney *U* test, as appropriate. A one-way analysis of variance (ANOVA) was used for multiple group comparisons. Correlations between variables were analyzed using Pearson's correlation test. Univariate and multivariate linear regression analyses were performed to investigate the association between echocardiographic and CCTA findings and the LVGLS. After adjusting for age, LVEF, LV mass index, and EAT volume, the parameters included in the models were obstructive CAD, CACS, SIS, and SSS. The CACS was log-transformed for the analysis. Statistical significance was set at a 2-sided *P* value of  $< 0.05$ .

## 3. Results

All patients had preserved LVEF of  $\geq 50\%$ , but without LV regional wall motion abnormalities. Table 1 shows the characteristics of all the study patients ( $n = 169$ ). The mean age of the study patients was  $67 \pm 13.6$  years and 59% were male. Approximately 70% of the patients had hypertension and dyslipidemia and 25% had diabetes mellitus.

The TTDE parameters are listed in Table 2. All patients had a preserved LVEF  $\geq 50\%$ , and the mean LVEF was 61% (53–67%). Mean LVGLS was  $-18.7\%$  ( $-20.5\% - -16.9\%$ ). The CCTA results are listed in Table 2. On CCTA, 53 patients (31.3%) had no visible CAD. For the remaining patients, non-obstructive CAD (1% to 49% stenosis) was present in 66 patients (39.0%), whereas obstructive CAD, defined as the presence of  $\geq 50\%$  diameter stenosis, was detected in 50 patients (29.6%). Among the patients with obstructive CAD, 10 (5.9%) exhibited  $\geq 50\%$  stenosis in multivessel CAD. Mean SSS and SIS were 2.0 (0–5) and 4.0 (0–36), respectively, while mean EAT volume was 116.1 mL ( $22.9-282.5$  mL).

Fig. 2 shows the LVGLS values stratified by CAD categories. LVGLS

**Table 1**  
Baseline characteristics.

	n = 169
Age, n (%)	67 (53–75)
Male, n (%)	100 (59%)
Smoking, n (%)	36 (21%)
Body mass index, kg/m <sup>2</sup>	23.2 (21.4–25.6)
Systolic blood pressure, mmHg	139 (127–155)
Diastolic blood pressure, mmHg	78 (70–89)
Heart rate, bpm	73 (66–82)
<b>Comorbidity</b>	
Hypertension, n (%)	121 (72%)
Diabetes, n (%)	42 (25%)
Dyslipidemia, n (%)	120 (71%)
<b>Medication at index CCTA examination</b>	
Calcium channel blocker, n (%)	58 (34%)
ACE inhibitor or ARB, n (%)	38 (23%)
$\beta$ -blocker, n (%)	7 (4.1%)
Statin, n (%)	44 (26%)
<b>Laboratory tests</b>	
Hemoglobin, g/dl	$13.9 \pm 2.3$
eGFR, ml/min/1.73 m <sup>2</sup>	$50.6 \pm 20.8$
hs-CRP, g/dl	$0.03 \pm 0.68$
hs-Troponin T, pg/ml	$2.0 (1.0-4.8)$
LDL-cholesterol, mg/dl	123 (100–141)
HDL-cholesterol, mg/dl	65 (51–73)
Triglyceride, mg/dl	134 (81–161)

Values are presented mean  $\pm$  standard deviation, or median (inter-quartile range), or n (%).

ACE; angiotensin convert enzyme,  
ARB; angiotensin type1 receptor blocker,  
eGFR; estimated glomerular filtration rate  
LDL; Low Density Lipoprotein  
HDL; High Density Lipoprotein

**Table 2**  
Echocardiography and CCTA findings.

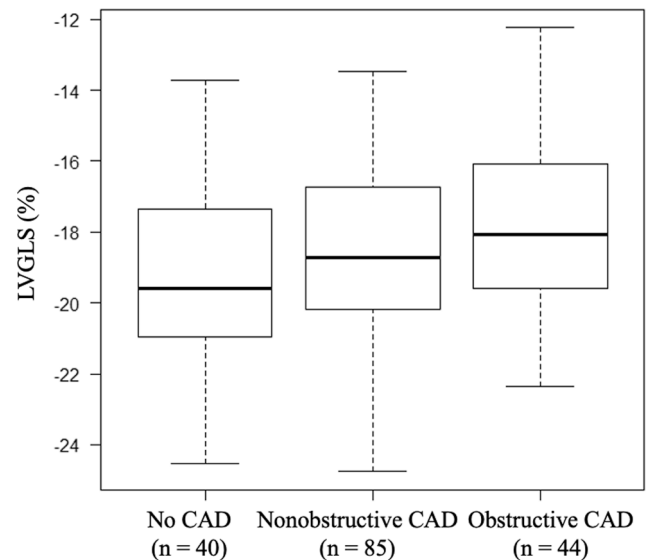
TTDE findings	
LVEF, %	61 (53–67)
LVEDD, mm	45.6 (34.3–56.1)
LVESD, mm	28.6 (15.7–39.0)
IVSWT, mm	8.3 (7.6–9.1)
LVPWT, mm	8.4 (7.5–9.0)
LA, mm	36.1 (32.7–39.7)
LVMI, g/mm <sup>2</sup>	61 (53–67)
Dct, msec	209.5 (175.4–242.7)
E/A ratio	0.91 (0.74–1.2)
E/e' ratio	9.93 (8.25–11.9)
TRPG, mmHg	20.6 (15.7–25.0)
LVGLS, %	–18.7 (–20.5 – –16.9)
CCTA and abdominal CT findings	
CACS	23,2 (0–4020)
0, n (%)	70 (41%)
1–99, n (%)	46 (27%)
100–399, n (%)	30 (18%)
>400, n (%)	23 (14%)
Non obstructive CAD, n (%)	85 (50%)
Obstructive CAD, n (%)	44 (26%)
LMCA, n (%)	7 (4.1%)
LAD, n (%)	34 (20%)
LCX, n (%)	17 (10%)
RCA, n (%)	12 (7.1%)
Multi-vessel CAD	10 (5.9)
SSS	2.0 (0–5)
SIS	4.0 (0–36)
EAT volume (ml)	116.1 (22.9–282.5)
Visceral adipose tissue area (ml)	93.7 (9.4–244.5)
Subcutaneous adipose tissue area (ml)	137.8 (3.6–709.0)

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

LVEF; left ventricular ejection fraction  
 LVEDd; left ventricular end-diastolic diameter  
 LVESD; left ventricular end-systolic diameter  
 IVSWT; Interventricular septum wall thickness  
 LVPWT; left ventricular posterior wall thickness  
 LA; Left Atrial  
 LVMI; Left ventricular mass index  
 Dct; Deceleration time  
 TRPG; tricuspid regurgitant pressure gradient  
 GLS; Global longitudinal strain  
 CAD; coronary artery disease  
 SSS; stenosis severity score  
 SIS; segment involvement score  
 EATV; Epicardial adipose tissue volume

tended to be higher in obstructive CAD ( $-17.9 \pm 2.7$  %) and even in nonobstructive CAD ( $-18.4 \pm 2.6$ %) as compared to that of no CAD patients ( $-19.3 \pm 2.4$ %) ( $p = 0.050$ , one-way ANOVA). We evaluated the correlations between the LVGLS and SSS, SIS, and EAT volumes (Fig. 3). Pearson's correlation analysis showed that there was a significant correlation between LVGLS and SSS ( $r = 0.25$ ,  $p = 0.001$ ), SIS ( $r = 0.24$ ,  $p = 0.002$ ), and EAT volume ( $r = 0.19$ ,  $p = 0.017$ ). There were no significant correlations between the location of obstructive CAD and LVGLS.

Univariate linear regression analysis demonstrated that there was no significant association of hypertension ( $\beta$ , 0.28; 95% confidence interval [CI],  $-0.69$ – $1.25$ ;  $p = 0.57$ ), diabetes mellitus ( $\beta$ , 0.91; 95%CI,  $-0.01$ – $1.83$ ;  $p = 0.054$ ), dyslipidemia ( $\beta$ , 0.79; 95%CI,  $-0.11$ – $1.70$ ;  $p = 0.08$ ) or chronic kidney disease ( $\beta$ ,  $-0.09$ ; 95%CI,  $-1.01$ – $0.81$ ;  $p = 0.83$ ) with LVGLS. Table 3 shows the univariate and multivariate linear regression analyses for the relationship between LVGLS and clinical parameters, TTDE, and CCTA findings. In the multivariable model, LVEF, LV mass index, and EAT volume were independently associated with LVGLS; however, obstructive CAD was not (Model 1 in Table 3). In contrast, the multivariable models demonstrated that SSS (model 3) and SIS (model 4) were positively correlated with LVGLS, independent of



**Fig. 2.** Association of LVGLS with patients with CAD stratified by CAD categories.

other parameters.

#### 4. Discussion

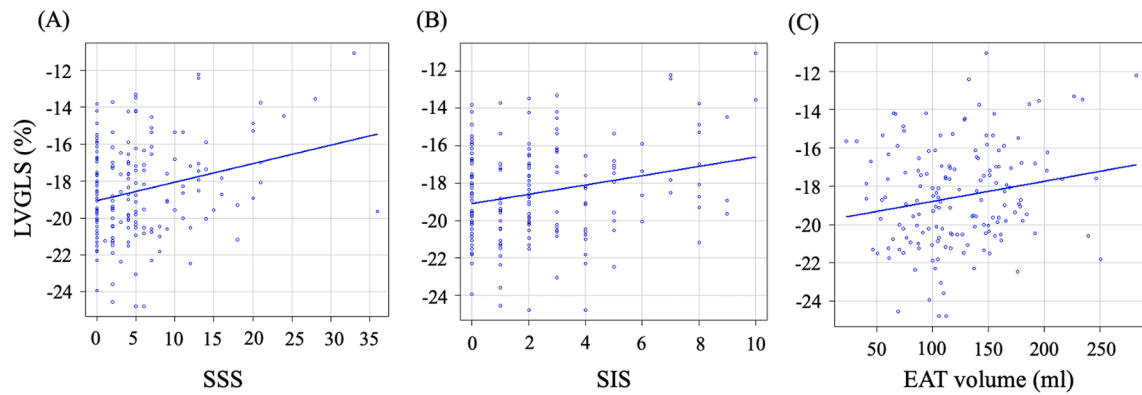
In this study, using CCTA and TTDE, we found a significant association between EAT volume and LVGLS assessed using speckle echocardiography in patients with preserved LVEF without LV regional wall motion abnormalities. Furthermore, semi-quantification of CAD extent or severity was significantly associated with LVGLS, even after adjusting for age, EAT volume, LVEF, and LV mass index. Our observations indicate that assessment of both the extent of CAD and EAT volume is crucial for risk stratification of patients at a higher risk of LV dysfunction in this population.

##### 4.1. CAD as a cause of LV dysfunction

The mechanisms mediating the increased risk of subclinical LV dysfunction are multifactorial. It has been well established that CAD is an underlying cause of not only heart failure with reduced ejection fraction (HFrEF) but also heart failure with preserved ejection fraction (HFpEF) [5,6,22]. Hwang et al. demonstrated that patients with HFpEF with angiographically proven CAD exhibited a higher risk of LV function deterioration than those without [22]. However, there is limited knowledge regarding whether CAD is associated with subclinical LV dysfunction.

Several potential mechanisms have been proposed to explain the association between CAD and subclinical LV dysfunctions [7]. A recent study conducted by Rush et al. demonstrated that the majority of patients with HFpEF exhibited epicardial obstructive CAD, CMD, or both [23]. Stankovic et al. demonstrated that critical coronary stenosis can cause LVGLS deterioration [10]. In line with this, our findings expand previous knowledge of the association between CAD, even in non-obstructive CAD, and subclinical LV dysfunction by highlighting the importance of the extent and severity of CAD. Impairment of LVGLS in patients with nonobstructive CAD may be explained by CMD, which is well correlated with LVGLS [24,25]. Identifying patients with non-obstructive CAD who are at a higher risk of cardiovascular events and heart failure has attracted attention. Nakanishi et al. demonstrated that impairment of the coronary flow reserve, a marker of CMD, provides prognostic value for ACS and heart failure in patients without obstructive CAD in the left ascending coronary artery on CCTA [26]. Given the technical limitations of noninvasive assessment of CMD and the





**Fig. 3.** Correlations between CAD extent or EAT volume and LVGLS. Spearman correlation demonstrated a significant correlation between SSS and LVGLS (A), between SIS and LVGLS (B), and between EAT volume and LVGLS (C).

**Table 3**  
Linear regression models for determinants of LVGLS.

Variable	Univariate model		Multivariable model 1		Multivariable model 2		Multivariable model 3		Multivariable model 4	
	Beta ( 95%CI )	P	Beta ( 95%CI )	P	Beta ( 95% CI )	P	Beta ( 95% CI )	P	Beta ( 95% CI )	P
LVEF, per 1% increase	-7.04 (-12.34–1.75)	0.009	-17.0 (-20.9 – -13.1)	0.015	-6.50 (-11.87–1.13)	0.017	-6.04 (-11.21 – -0.87)	0.022	-6.08 (11.2–0.87)	0.022
Age, per 1 year increase	-0.030 (-0.061–0.0002)	0.050	-0.02 (-0.05–0.005)	0.103	-0.04 (-0.07 – -0.004)	0.029	-0.04 (-0.07 – -0.012)	0.006	-0.04 (-0.07–0.01)	0.007
Male	1.696 (0.88–2.51)	<0.001	1.06 (0.20–1.92)	0.016	0.99 (0.13–1.85)	0.024	0.68 (0.16–1.53)	0.112	0.74 (-0.10–1.60)	0.085
LVMI, per 1 g/m <sup>2</sup> increase	0.042 (0.0168–0.067)	0.001	0.03 (0.01–0.06)	0.002	0.034 (0.01–0.05)	0.005	0.03 (0.01–0.05)	0.003	0.03 (0.01–0.05)	0.003
EAT volume, per 1 mL increase	0.011 (0.002–0.019)	0.015	0.010 (0.002–0.0195)	0.021	0.01 (0.001–0.019)	0.024	0.009 (0.0005–0.01)	0.039	0.009 (0.0004–0.01)	0.039
Obstructive CAD	0.368 (-0.552–1.288)	0.430	0.54 (-0.33–1.42)	0.224						
Log (CACS + 1)	0.230 (-0.139–0.600)	0.220			0.35 (-0.06–0.76)	0.097				
SSS, per 1 increase	0.115 (0.054–0.176)	<0.001					0.12 (0.05–0.18)	<0.001		
SIS, per 1 increase	0.297 (0.137–0.457)	<0.001							0.27 (0.10–0.44)	0.001

CAD; Coronary artery disease  
SSS; stenosis severity score  
SIS; segment involvement score  
EATV; Epicardial adipose tissue volume  
LVMI; Left ventricular mass index

advantages of widespread CCTA imaging in daily clinical practice, CAD extent may offer an explanation for subclinical LV dysfunction in the pre-heart failure population.

**4.2. Markers in identifying subclinical LV dysfunction**

Numerous studies have shown that EAT plays a key role in the pathophysiology of cardiovascular diseases [12,19]. Maimaituxun et al. demonstrated that increased EAT volume is associated with LVGLS impairment (≤18%) [27]. Although the underlying mechanisms between EAT accumulation and LV dysfunction remain unclear, increased inflammation, fibrosis, and autonomic dysregulation have been implicated as potential mechanisms linking EAT to LV dysfunction [28]. LVGLS assessed by speckle-tracking echocardiography is a marker of subclinical LV dysfunction, with diagnostic and prognostic implications for pre-heart failure [8,9].

A key challenge is the identification of patients at a higher risk of developing LV dysfunction leading to heart failure. In our study, comorbidities were not found to be associated with LVGLS deterioration.

The biomarker or imaging marker approach is an interesting perspective for understanding the potential mechanisms of epicardial fat accumulation and myocardial fibrosis and the risk stratification of patients with HFpEF [12–14]. Seo et al. demonstrated that HFpEF patients with CAD had greater deterioration in left ventricular ejection fraction and mitral annulus early diastolic velocity (e'), indicating that myocardial ischemia with a positive stress test may contribute to greater deterioration of diastolic dysfunction [29]. Harada et al. have shown that levels of serum fatty-acid binding protein 4, which is highly expressed in adipocytes and secreted in response to lipolytic signals, correlate with cardiac structural and functional abnormalities in patients with HFpEF, providing prognostic implications [30]. Further studies are required to investigate the clinical significance of LVGLS in association with biomarkers in patients with CAD leading to HFpEF.

**4.3. Therapeutic implication for identification of subclinical LV dysfunction**

Over the past few decades, large clinical studies have shown that

pharmacological therapies, including renin-angiotensin system inhibitors,  $\beta$ -blockers, sodium-glucose co-transporter (SGLT)-2 inhibitors, mineral corticoid receptor antagonists, and angiotensin receptor-neprilysin inhibitors, are effective in the treatment of patients with HFpEF. However, pharmacological therapeutic strategies for HFpEF are limited [31]. Sato et al. demonstrated that SGLT2 inhibitors can reduce EAT volume with a correlation between EAT volume, body weight, and inflammatory biomarkers [32]. Considering the significant associations between EAT, CAD extent and severity, and subclinical LV dysfunction, our observations suggest that EAT could serve as a potential therapeutic target to prevent subclinical LV dysfunction leading to cardiovascular events. Further studies are necessary to investigate whether medical therapy targeting the EAT can prevent the deterioration of LV function and cardiovascular events in this population.

#### 4.4. Study limitations

This study had some limitations. First, there may have been selection bias because this was an observational study consisting of a relatively small number of patients who underwent CCTA and TTDE. Previous studies have demonstrated that HFpEF includes multiple etiologies of heart failure. Phenotyping of the disease according to etiology can provide further insights into the pathophysiology and management of HFpEF [16]. Furthermore, our study consisted of patients with normal weight/overweight rather than obese patients who are well known to have HFpEF [33]. Second, this study did not include patients with atrial fibrillation who were not suitable for LVGLS assessment using speckle-tracking echocardiography. In addition, focal LV wall motion abnormalities contribute to the impairment of LVGLS, and this study did not include patients with focal asynergy of the LV [10]. Therefore, our observations cannot be generalized to patients with atrial fibrillation or regional wall motion abnormalities caused by severe coronary luminal stenosis. Finally, CMD, especially HFpEF, was not assessed as a potent cause of subclinical HF in the present study. CMD can account for up to two-thirds of symptomatic ischemic heart disease patients without epicardial coronary artery stenosis [16]. Löffler et al. demonstrated that HFpEF patients had a higher prevalence of CMD and diffuse fibrosis with decreased exercise tolerance than healthy controls, although LVGLS tended to be higher in the latter [34]. Further prospective studies are warranted to comprehensively assess the causal effects of CAD extent, EAT accumulation, and CMD on heart failure development.

#### 5. Conclusion

The present study demonstrates that EAT volume and CAD extent, even in the less advanced stage of atherosclerosis, can influence subclinical LV function. CCTA may help to investigate the underlying causes of subclinical LV dysfunction in patients with preserved LVEF without LV wall motion abnormalities.

#### Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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#### References

- [1] J. Knuuti, W. Wijns, A. Saraste, D. Capodanno, E. Barbato, C. Funck-Brentano, E. Prescott, R.F. Storey, C. Deaton, T. Cuisset, S. Agewall, K. Dickstein, T. Edvardsen, J. Escaned, B.J. Gersh, P. Svitil, M. Gilard, D. Hasdai, R. Hatala, F. Mahfoud, J. Masip, C. Muneretto, M. Valgimigli, S. Achenbach, J.J. Bax, 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndrome, *Eur. Heart J.* 41 (2020) 407–477, <https://doi.org/10.1093/eurheartj/ehz425>.
- [2] D.M. Lloyd-Jones, M.G. Larson, E.P. Leip, A. Beiser, R.B. D'Agostino, W.B. Kannel, J.M. Murabito, R.S. Vasan, E.J. Benjamin, D. Levy, Lifetime risk for developing congestive heart failure: the framingham heart study, *Circulation.* 106 (2002) 3068–3072, <https://doi.org/10.1161/01.cir.0000039105.49749.6f>.
- [3] A. Lala, A.S. Desai, The role of coronary artery disease in heart failure, *Heart Failure.* Clin. 10 (2014) 353–365, <https://doi.org/10.1016/j.hfc.2013.10.002>.
- [4] S.S. Virani, A. Alonso, E.J. Benjamin, M.S. Bittencourt, C.W. Callaway, A.P. Carson, A.M. Chamberlain, A.R. Chang, S. Cheng, F.N. Delling, L. Djousse, M.S.V. Elkind, J. F. Ferguson, M. Fornage, S.S. Khan, B.M. Kissela, K.L. Knutson, T.W. Kwan, D. T. Lackland, T.T. Lewis, J.H. Lichtman, C.T. Longenecker, M.S. Loop, P.L. Lutsey, S. S. Martin, K. Matsushita, A.E. Moran, M.E. Mussolino, A.M. Perak, W.D. Rosamond, G.A. Roth, U.K.A. Sampson, G.M. Satou, E.B. Schroeder, S.H. Shah, C.M. Shay, N. L. Spartano, A. Stokes, D.L. Tirschwell, L.B. VanWagner, C.W. Tsao, S.S. Wong, D. G. Heard, Heart disease and stroke statistics—2020 update: a report from the American Heart Association, 2020, *Circulation.* 141 (2020) e139–e596, <https://doi.org/10.1161/CIR.0000000000000757>.
- [5] D. Maragiannis, R.C. Schutt, N.L. Gramze, K. Chaikriangkrai, K. McGregor, K. Chin, F. Nabi, S.H. Little, S.F. Nagueh, S.M. Chang, Association of left ventricular diastolic dysfunction with subclinical coronary atherosclerotic disease burden using coronary artery calcium scoring, *Thromb.* 22 (2015) 1278–1286, <https://doi.org/10.5551/jat.29454>.
- [6] S.M. Dunlay, V.L. Roger, M.M. Redfield, Epidemiology of heart failure with preserved ejection fraction, *Nat. Rev. Cardiol.* 14 (2017) 591–602, <https://doi.org/10.1038/nrcardio.2017.65>.
- [7] J.E. John, B. Claggett, H. Skali, S.D. Solomon, J.W. Cunningham, K. Matsushita, S. H. Konecny, D.W. Kitzman, T.H. Mosley, D. Clark, P.P. Chang, A.M. Shah, Coronary artery disease and heart failure with preserved ejection fraction: the ARIC study, *J. Am. Heart Assoc.* 11 (2022), <https://doi.org/10.1161/JAHA.121.021660>.
- [8] T. Kuznetsova, N. Cauwenberghs, J. Knez, W.-Y. Yang, L. Herbots, J. D'hooge, F. Haddad, L. Thijs, J.-U. Voigt, J.A. Staessen, Additive prognostic value of left ventricular systolic dysfunction in a population-based cohort, *Circ. Cardiovasc. Imag.* 9 (2016). <https://doi.org/10.1161/CIRCIMAGING.116.004661>.
- [9] J.J. Park, J.B. Park, J.H. Park, G.Y. Cho, Global longitudinal strain to predict mortality in patients with acute heart failure, *J. Am. Coll. Cardiol.* 71 (2018) 1947–1957, <https://doi.org/10.1016/j.jacc.2018.02.064>.
- [10] I. Stankovic, B. Putnikovic, R. Cvjetan, P. Milicevic, M. Panic, T. Kalezic-Radmili, T. Mandaric, R. Vidakovic, V. Cvorovic, A.N. Neskovic, Visual assessment vs. strain imaging for the detection of critical stenosis of the left anterior descending coronary artery in patients without a history of myocardial infarction, *Eur. Heart J. Cardiovasc. Imag.* 16 (2015) 402–409, <https://doi.org/10.1093/ehjci/jeu206>.
- [11] K.M. Abdelrahman, M.Y. Chen, A.K. Dey, R. Virmani, A.V. Finn, R.Y. Khamis, A. D. Choi, J.K. Min, M.C. Williams, A.J. Buckler, C.A. Taylor, C. Rogers, H. Samady, C. Antoniadis, L.J. Shaw, M.J. Budoff, U. Hoffmann, R. Blankstein, J. Narula, N. N. Mehta, Coronary computed tomography angiography from clinical uses to emerging technologies: JACC state-of-the-art review, *J. Am. Coll. Cardiol.* 76 (2020) 1226–1243, <https://doi.org/10.1016/j.jacc.2020.06.076>.
- [12] K. Nakanishi, S. Fukuda, A. Tanaka, K. Otsuka, H. Taguchi, J. Yoshikawa, K. Shimada, Epicardial adipose tissue accumulation is associated with renal dysfunction and coronary plaque morphology on multidetector computed tomography, *Circ. J.* 80 (2015) 196–201, <https://doi.org/10.1253/circj.CJ-15-0477>.
- [13] A.M. Ansaldo, F. Montecucco, A. Sahebkar, F. Dallegrì, F. Carbone, epicardial adipose tissue and cardiovascular diseases, *Int. J. Cardiol.* 278 (2019) 254–260, <https://doi.org/10.1016/j.ijcard.2018.09.089>.
- [14] C.J. Nalliah, J.R. Bell, A.J.A. Raaijmakers, H.M. Waddell, S.P. Wells, G. B. Bernasocchi, M.K. Montgomery, S. Binny, T. Watts, S.B. Joshi, E. Lui, C.B. Sim, M. Larobina, M. O'Keefe, J. Goldblatt, A. Royle, G. Lee, E.R. Porrello, M.J. Watt, P. M. Kistler, P. Sanders, L.M.D. Delbridge, J.M. Kalman, epicardial adipose tissue accumulation confers atrial conduction abnormality, *J. Am. Coll. Cardiol.* 76 (2020) 1197–1211, <https://doi.org/10.1016/j.jacc.2020.07.017>.
- [15] J.L. Cavalcante, B.K. Tamarappoo, R. Hachamovitch, D.H. Kwon, M.C. Alraies, S. Halliburton, P. Schoenhagen, D. Dey, D.S. Berman, T.H. Marwick, Association of epicardial fat, hypertension, subclinical coronary artery disease, and metabolic syndrome with left ventricular diastolic dysfunction, *J. Cardiol.* 110 (2012) 1793–1798, <https://doi.org/10.1016/j.amjcard.2012.07.045>.
- [16] M.M. Zawadzka, M. Grabowski, A. Kaplon-Cieślicka, Phenotyping in heart failure with preserved ejection fraction: a key to find effective treatment, *Adv. Clin. Exp. Med.* 31 (2022) 1163–1172, <https://doi.org/10.17219/acem/149728>.
- [17] K. Nakanishi, S. Fukuda, A. Tanaka, K. Otsuka, H. Taguchi, K. Shimada, Relationships between periventricular epicardial adipose tissue accumulation, coronary microcirculation, and left ventricular diastolic dysfunction, *Can. J. Cardiol.* 33 (2017) 1489–1497, <https://doi.org/10.1016/j.cjca.2017.08.001>.
- [18] K. Otsuka, K. Nakanishi, K. Shimada, H. Nakamura, H. Inanami, H. Nishioka, K. Fujimoto, N. Kasayuki, M. Yoshiyama, Ankle-brachial index, arterial stiffness, and biomarkers in the prediction of mortality and outcomes in patients with end-stage kidney disease, *Cardiol.* 42 (2019) 656–662, <https://doi.org/10.1002/clc.23188>.
- [19] H. Yamaura, K. Otsuka, H. Ishikawa, K. Shirasawa, D. Fukuda, N. Kasayuki, Determinants of non-calcified low-attenuation coronary plaque burden in patients without known coronary artery disease: a coronary CT angiography study, *Front. Cardiovasc. Med.* 9 (2022), 824470, <https://doi.org/10.3389/fcvm.2022.824470>.

- [20] K. Otsuka, H. Ishikawa, Y. Kono, S. Oku, H. Yamaura, K. Shirasawa, K. Hirata, K. Shimada, N. Kasayuki, D. Fukuda, Aortic arch plaque morphology in patients with coronary artery disease undergoing coronary computed tomography angiography with wide-volume scan, *Coronary Artery Dis.* 33 (2022) 531–539, <https://doi.org/10.1097/MCA.0000000000001171>.
- [21] H.S. Hecht, M.J. Blaha, E.A. Kazerooni, R.C. Cury, M. Budoff, J. Leipsic, L. Shaw, CAC-DRS: coronary artery calcium data and reporting system. expert consensus document of the Society of Cardiovascular Computed Tomography (SCCT), *J. Cardiovasc. Comput. Tomogr.* 12 (2018) 185–191, <https://doi.org/10.1016/j.jcct.2018.03.008>.
- [22] S.-J. Hwang, V. Melenovsky, B.A. Borlaug, Implications of coronary artery disease in heart failure with preserved ejection fraction, *J. Am. Coll. Cardiol.* 63 (2014) 2817–2827, <https://doi.org/10.1016/j.jacc.2014.03.034>.
- [23] C.J. Rush, C. Berry, K.G. Oldroyd, J.P. Rocchiccioli, M.M. Lindsay, R.M. Touyz, C.L. Murphy, T.J. Ford, N. Sidik, M.B. McEntegart, N.N. Lang, P.S. Jhund, R.T. Campbell, J.J. V McMurray, M.C. Petrie, Prevalence of coronary artery disease and coronary microvascular dysfunction in patients with heart failure with preserved ejection fraction., 6 (2021) 1130–1143. <<https://doi.org/10.1001/jamacardio.2021.1825>>.
- [24] T.S. Clemmensen, B.B. Løgstrup, H. Eiskjaer, S.H. Poulsen, Coronary flow reserve predicts longitudinal myocardial deformation capacity in heart transplant patients, *Echocardiography.* 33 (2016) 562–571, <https://doi.org/10.1111/echo.13123>.
- [25] V. Sucato, A.R. Galassi, S. Novo, A. Saladino, S. Evola, G. Novo, **Correlation between longitudinal strain analysis and coronary microvascular dysfunction in patients with heart failure with preserved ejection fraction**, *Microcirculation.* 27 (2020) e12605.
- [26] K. Nakanishi, S. Fukuda, K. Shimada, C. Miyazaki, K. Otsuka, K. Maeda, R. Miyahana, T. Kawarabayashi, H. Watanabe, J. Yoshikawa, M. Yoshiyama, Impaired coronary flow reserve as a marker of microvascular dysfunction to predict long-term cardiovascular outcomes, acute coronary syndrome, and development of heart failure, *Circ J.* 76 (2012) 1958–1964, <https://doi.org/10.1253/circj.cj-12-0245>.
- [27] G. Maimaituxun, K. Kusunose, H. Yamada, D. Fukuda, S. Yagi, Y. Torii, N. Yamada, T. Soeki, H. Masuzaki, M. Sata, M. Shimabukuro, Deleterious effects of epicardial adipose tissue volume on global longitudinal strain in patients with preserved left ventricular ejection fraction, *Front. Cardiovasc. Med.* 7 (2020) 607825. <<https://doi.org/10.3389/fcvm.2020.607825>>.
- [28] G. Iacobellis, Epicardial adipose tissue in contemporary cardiology, *Nat. Rev. Cardiol.* (2022) 1–14, <https://doi.org/10.1038/s41569-022-00679-9>.
- [29] J.H. Seo, D. Hong, T. Youn, S.H. Lee, K.H. Choi, D. Kim, T.K. Park, J.M. Lee, Y. Bin Song, J.O. Choi, J.Y. Hahn, S.H. Choi, H.C. Gwon, E.S. Jeon, J.H. Yang, Prognostic implications of coronary artery disease and stress tests in patients with elevated left ventricular filling pressure and preserved ejection fraction, *Front. Cardiovasc. Med.* 9 (2022), <https://doi.org/10.3389/fcvm.2022.955731>.
- [30] T. Harada, H. Sunaga, H. Sorimachi, K. Yoshida, T. Kato, K. Kurosawa, T. Nagasaka, N. Koitabashi, T. Iso, M. Kurabayashi, M. Obokata, Pathophysiological role of fatty acid-binding protein 4 in Asian patients with heart failure and preserved ejection fraction, *ESC Heart Fail.* 7 (2020) 4256–4266, <https://doi.org/10.1002/ehf2.13071>.
- [31] S.D. Anker, J. Butler, G. Filippatos, J.P. Ferreira, E. Bocchi, M. Böhm, H.-P. Brunner-La Rocca, D.-J. Choi, V. Chopra, E. Chuquiure-Valenzuela, N. Giannetti, J.E. Gomez-Mesa, S. Janssens, J.L. Januzzi, J.R. Gonzalez-Juanatey, B. Merkely, S. J. Nicholls, S.V. Perrone, I.L. Piña, P. Ponikowski, M. Senni, D. Sim, J. Spinar, I. Squire, S. Taddei, H. Tsutsui, S. Verma, D. Vinereanu, J. Zhang, P. Carson, C.S. P. Lam, N. Marx, C. Zeller, N. Sattar, W. Jamal, S. Schnaidt, J.M. Schnee, M. Brueckmann, S.J. Pocock, F. Zannad, M. Packer, Empagliflozin in heart failure with a preserved ejection fraction, *N. Engl. J. Med.* 385 (2021) 1451–1461, <https://doi.org/10.1056/NEJMoa2107038>.
- [32] T. Sato, Y. Aizawa, S. Yuasa, S. Kishi, K. Fuse, S. Fujita, Y. Ikeda, H. Kitazawa, M. Takahashi, M. Sato, M. Okabe, The effect of dapagliflozin treatment on epicardial adipose tissue volume, *Cardiovasc. Diabetol.* 17 (2018) 6, <https://doi.org/10.1186/s12933-017-0658-8>.
- [33] J. He, W. Yang, W. Wu, X. Sun, S. Li, G. Yin, B. Zhuang, J. Xu, D. Zhou, Y. Zhang, Y. Wang, L. Zhu, P. Sharma, A. Sirajuddin, Z. Teng, F. Kureshi, S. Zhao, M. Lu, Clinical features, myocardial strain and tissue characteristics of heart failure with preserved ejection fraction in patients with obesity: a prospective cohort study, *Eclinical Med.* 55 (2023), 101723, <https://doi.org/10.1016/j.eclinm.2022.101723>.
- [34] A.I. Löffler, J.A. Pan, P.C. Balfour, P.W. Shaw, Y. Yang, M. Nasir, D.A. Auger, F. H. Epstein, C.M. Kramer, L.M. Gan, M. Salerno, Frequency of coronary microvascular dysfunction and diffuse myocardial fibrosis (Measured by Cardiovascular Magnetic Resonance) in patients with heart failure and preserved left ventricular ejection fraction, *Am. J. Cardiol.* 124 (2019) 1584–1589, <https://doi.org/10.1016/j.amjcard.2019.08.011>.