ESC European Society of Cardiology

European Heart Journal Open (2023) **3**, 1–5
https://doi.org/10.1093/ehjopen/oeac082

**SHORT REPORT**
*Coronary artery disease*

# Epicardial fat accumulation and left heart remodelling in patients with chronic coronary syndrome

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*Received 29 September 2022; revised 15 November 2022; accepted 16 December 2022; online publish-ahead-of-print 17 December 2022*

Handling Editor: Maciej Banach

**Aims**

Patients with chronic coronary syndrome (CCS) suffer from subsequent cardiovascular events, even after complete revascularization; thus, elucidation of the underlying pathophysiological mechanisms is required. Epicardial adipose tissue (EAT) is increasingly recognized as a metabolically active organ with a key role in the pathogenesis of metabolic-related cardiac diseases. The present study investigated the association between EAT burden and left heart remodelling in patients with CCS.

**Methods and results**

We studied 267 CCS patients (210 men; 71 ± 9 years) with complete revascularization and normal left ventricular (LV) ejection fraction who underwent follow-up echocardiography. All patients underwent the measurement of EAT thickness and speckle-tracking analysis to evaluate LV global longitudinal strain (LVGLS) and left atrial (LA) phasic strain. The mean EAT thickness was 5.0 ± 1.8 mm. Age, sex, body mass index, and diabetes mellitus were independently associated with EAT thickness (all $P < 0.05$). Multivariable linear regression analysis demonstrated that EAT thickness was significantly associated with LV mass index, early diastolic mitral annular velocity, and LA conduit strain independent of age, sex, and cardiovascular risk factors (all $P < 0.05$). On the other hand, there was no relationship between EAT thickness and LV systolic parameters including LV ejection fraction and LVGLS.

**Conclusion**

CCS patients with increased EAT thickness had unfavourable left heart remodelling. The assessment of EAT thickness by echocardiography may have clinical utility as a simple surrogate to aid in risk stratification for impaired left heart function in CCS patients.

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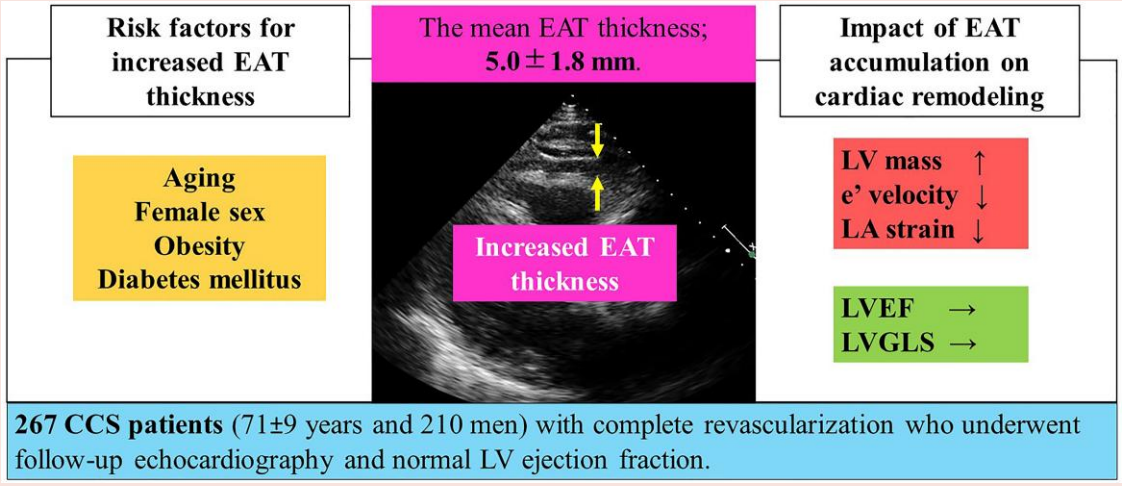
## Graphical Abstract




**Keywords** Chronic coronary syndrome • Epicardial adipose tissue • Left heart remodelling • Speckle-tracking echocardiography

# Introduction

Patients with chronic coronary syndrome (CCS) are at higher risk of various form of cardiovascular disease, even with adequate revascularization and optimal medical therapy;[1] thus, elucidation of the underlying pathophysiological mechanisms is needed. Recently, particular attention has been given to epicardial adipose tissue (EAT) accumulation in the context of metabolic-related cardiac diseases.[2,3] However, the association between EAT accumulation and left ventricular(LV)/left atrial (LA) functional remodelling in patients with CCS has not been studied. LV global longitudinal strain (LVGLS) and LA phasic strain derived from speckle-tracking echocardiography emerge as highly sensitive measures to unmask subclinical left heart impairment.[4] The aim of the present study was to investigate the association between EAT and left heart remodelling in patients with CCS with complete percutaneous coronary intervention (PCI) and preserved LV ejection fraction (LVEF) using conventional and speckle-tracking echocardiography.

# Methods

Consecutive 476 patients with CCS who had completed elective coronary revascularization and undergone follow-up echocardiography at the University of Tokyo Hospital between 2014 and 2016 were retrospectively recruited. Patients with a history of myocardial infarction ($n = 62$), coronary artery bypass grafting surgery ($n = 16$), atrial fibrillation or atrial flutter ($n = 34$), congenital heart disease ($n = 2$), LVEF <50% or significant valvular heart disease ($n = 34$), poor echocardiographic image quality for EAT measurement including patients with pericardial effusion ($n = 46$), lacking clinical information ($n = 1$), and inadequate image quality for strain analysis ($n = 14$) were excluded. Thus, 267 Asian patients with CCS who met the study criteria were included for the analysis. The Institutional Review Board of the University of Tokyo approved the study.

Measurement of EAT thickness was performed by two experienced cardiologists (K.N. and K.H.) with at least 7 years of experience who were unaware of the clinical data. Epicardial fat was identified as the echo-free space between the outer wall of the myocardium and the visceral layer of the pericardium, and its thickness was measured perpendicularly on the free wall of the right ventricle at end-systole according to the current American Society of Echocardiography recommendation (*Figure 1*).[5] We further performed additional measurement of EAT thickness from short-axis images in randomly selected 30 patients and found good correlation between the two views with Pearson's correlation coefficient of 0.88 and $-0.4 \pm 2.5$ mm (mean $\pm$ 1.96 SD) in Bland–Altman analysis. Speckle-tracking analysis was performed offline using vendor-independent commercially available software (2D Cardiac Performance Analysis; Tomtec Imaging System, Germany). LVGLS was calculated by averaging the negative peak of longitudinal strain from all three apical views including the four-chamber, two-chamber, and long-axis views, and LA phasic strain was obtained by averaging the peak values of six LA segmental strains from the apical two- and four- chamber views.[4]

Categorical variables are presented as numbers and proportions, and continuous variables are presented as means $\pm$ standard deviations or median and interquartile range as appropriate. Association between clinical parameters and EAT thickness was assessed by univariable and multivariable linear regression analysis. Univariable and multivariable linear regression analyses were also carried out to identify the association of EAT thickness as a continuous variable with LV/LA morphology and function, adjusting for potential covariates in a sequential fashion with two models: Model 1, adjustment for age and sex and Model 2, adjustment for age, sex, hypertension, hyperlipidaemia, diabetes mellitus, body mass index (BMI), smoking status, and estimated glomerular filtration rate (eGFR). A $P$ value of $<0.05$ was considered statistically significant. All analyses were performed with the JMP Pro 15 statistical software (SAS Institute, Inc, Cary, NC, USA).

# Results

*Table 1* shows the clinical characteristics and echocardiographic parameters of the study population. The mean age was 71 $\pm$ 9 years, and 210 (78.7%) were men. The mean EAT thickness was 5.0 $\pm$ 1.8 mm. Age, sex, BMI, hypertension, and diabetes mellitus were associated with EAT thickness by univariable linear regression analysis, while there was no relationship between the duration of statin therapy and EAT thickness. Multivariable linear regression analysis identified that older age, female gender, higher BMI, and diabetes mellitus were independently associated with increased EAT thickness.

The relationship between EAT thickness and LV morphology and function is shown in *Table 2*. EAT thickness was associated with LV mass index and early diastolic mitral annular velocity (e') in the age- and sex-adjusted

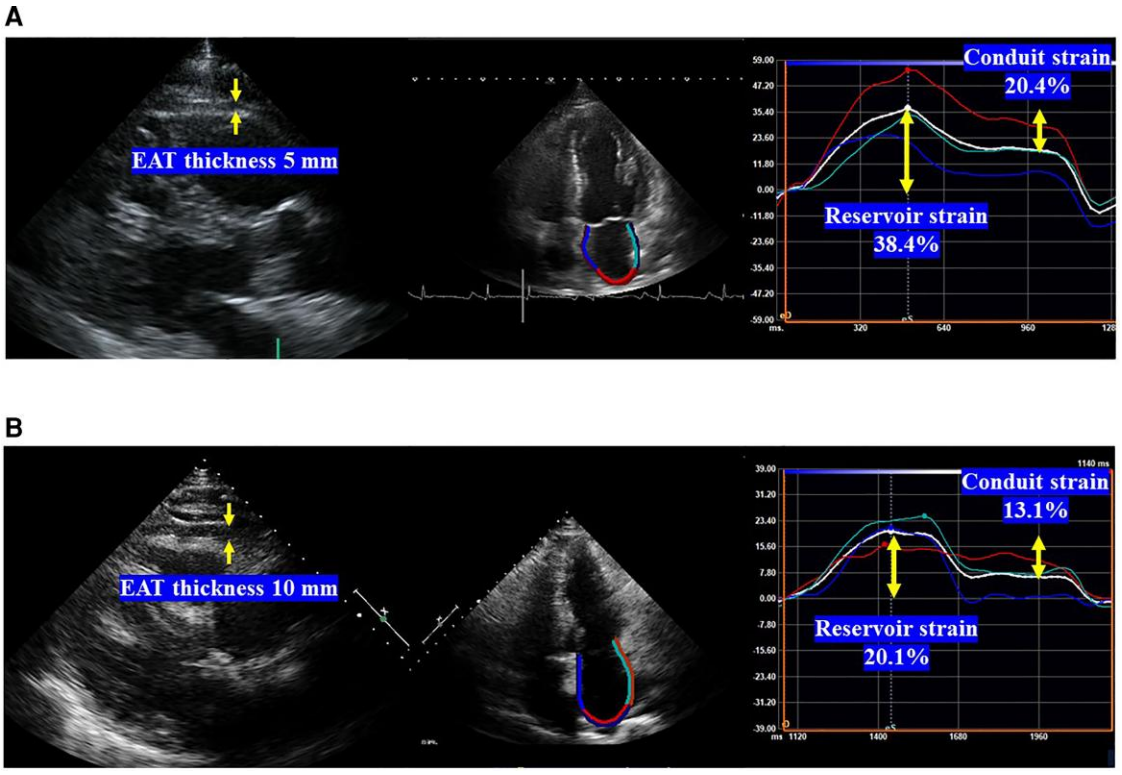



**Figure 1** Representative cases of chronic coronary syndrome patients with and without abnormal epicardial adipose tissue thickness. The lower case with abnormal epicardial adipose tissue thickness had left atrium dysfunction (*B*), whereas preserved left atrium function was observed in the upper case with normal epicardial adipose tissue thickness (*A*).

model (Model 1). In the multivariable model adjusted for age, sex, hypertension, hyperlipidaemia, diabetes mellitus, BMI, current smoking, and eGFR, EAT thickness remained independently associated with LV mass index (standardized β = 0.15, $P = 0.013$) and e′ (standardized β −0.18, $P = 0.005$; Model 2). However, EAT thickness was not associated with LV systolic parameters (i.e. LVEF and LVGLS).

As for the LA parameters, EAT thickness was associated with LA volume index, LA reservoir, and conduit strain in univariable analysis (all $P < 0.05$; *Table 2*). Multivariable model adjusted for age and sex attenuated the association between EAT accumulation and LA reservoir strain (standardized β −0.11, $P = 0.065$), whereas increased EAT thickness was related to larger LA volume index and reduced LA conduit strain (Model 1). Additional adjustment for cardiovascular risk factors and eGFR did not affect the independent association of EAT thickness with LA conduit strain (standardized β = −0.13, $P = 0.037$; Model 2). Representative cases are presented in *Figure 1*.

Excellent correlations were observed for the inter-observer variability of EAT thickness and strain measures in 15 randomly selected patients: $r = 0.88$ for EAT thickness, $r = 0.93$ for LVGLS, $r = 0.92$ for LA reservoir strain, $r = 0.91$ for LA conduit strain, and $r = 0.87$ for LA pump strain. According to the Bland–Altman analysis, inter-observer variability was 0.1 ± 2.3 mm for EAT thickness, 0.4 ± 1.7% for LVGLS, 0.8 ± 4.9% for LA reservoir strain, 0.7 ± 4.1% for LA conduit strain, and 0.1 ± 3.6% for LA pump strain (mean ± 1.96 SD, respectively).

# Discussion

In the present study, we comprehensively evaluated the association of EAT accumulation with LV/LA morphology and functional remodelling using conventional and speckle-tracking echocardiography in CCS patients and found that EAT accumulation was independently related to LV mass index, e′ and LA conduit strain. The underlying mechanisms by which EAT accumulation was associated with unfavourable left heart remodelling are not entirely clear, but we propose several potential explanations. First, adipocyte direct infiltration within LA/LV myocardium can cause LV and LA dysfunction.[6] Second, through paracrine transmission, pro-inflammatory, pro-oxidant, and pro-fibrotic cytokines from EAT diffuse into the myocardium, which may lead to unfavourable left heart remodeling.[2] Finally, impaired coronary microcirculation might be involved in our observation.[7] On the other hand, we did not find an association between EAT thickness and LV systolic parameters (i.e. LVEF and LVGLS). This may be partially explained by the fact that LV diastolic dysfunction precedes systolic dysfunction in metabolic-related cardiac remodelling. Indeed, increased EAT predominantly augmented the risk of HF with preserved LVEF rather than reduced LVEF in the Multi-Ethnic Study of Atherosclerosis.[8] Several limitations should be noted. First, measurement of EAT thickness was performed only by transthoracic echocardiography, which might not accurately reflect the total amount of EAT and its distribution. Second, we did not perform sample size calculation because of the retrospective nature of the study. Furthermore, echocardiography was performed at the physicians' discretion; therefore, the timing of echocardiography was varied depending on patients which might affect our observation. Third, the optimal cut-off values of LA/LV remodelling in the setting of CCS are not well established. Future studies are warranted to investigate the thresholds of echocardiographic parameters for the prediction of incident CV events. Finally, this study consisted of CCS patients after revascularization and preserved LVEF, which may limit the applicability of the results to CAD patients with different risk profiles, such as ischaemic cardiomyopathy. In

**Table 1 Characteristics and echocardiographic parameters of the study population**

| ***n* = 267** | |
|---|---|
| Age, years | 71 ± 9 |
| Men, *n* (%) | 210 (78.7) |
| Body mass index, kg/m$^2$ | 24.2 ± 3.6 |
| Systolic blood pressure, mmHg | 134 ± 19 |
| Diastolic blood pressure, mmHg | 70 ± 12 |
| Heart rate, beats/min | 67 ± 12 |
| Current smoking, *n* (%) | 14 (5.2) |
| Hypertension, *n* (%) | 250 (93.6) |
| Diabetes mellitus, *n* (%) | 135 (50.6) |
| Dyslipidaemia, *n* (%) | 251 (94.0) |
| Medications | |
| β blocker, *n* (%) | 120 (44.9) |
| RAS inhibitor, *n* (%) | 198 (74.2) |
| Calcium channel blocker, *n* (%) | 162 (60.7) |
| Statin, *n* (%) | 238 (89.1) |
| Oral anti-diabetic agents, *n* (%) | 109 (40.8) |
| Insulin, *n* (%) | 34 (12.7) |
| Laboratory data | |
| LDL cholesterol, mg/dL | 82 ± 23 |
| HDL cholesterol, mg/dL | 54 ± 16 |
| HbA1c, % | 6.5 ± 1.0 |
| eGFR, mL/min/1.73 m$^2$ | 60 ± 21 |
| PCI history | |
| Duration between TTE and PCI, years | 3.4 (0.9–6.4) |
| Number of treated vessels, *n* (%) | |
| 1 | 110 (41.2) |
| 2 | 105 (39.3) |
| 3 | 52 (19.5) |
| LMT lesion, *n* (%) | 29 (10.9) |
| LAD lesion, *n* (%) | 215 (80.5) |
| LCX lesion, *n* (%) | 115 (43.1) |
| RCA lesion, *n* (%) | 133 (49.8) |
| Two-dimensional echocardiography | |
| LV end-diastolic diameter, mm | 45.3 ± 5.2 |
| LV end-systolic diameter, mm | 28.6 ± 4.5 |
| LV ejection fraction, % | 61.4 ± 4.7 |
| LV mass index, g/m$^2$ | 86.5 ± 25.3 |
| E wave, cm/s | 64.4 ± 16.8 |
| A wave, cm/s | 81.0 ± 19.4 |
| E/A ratio | 0.83 ± 0.27 |
| e′ velocity, cm/s | 6.1 ± 1.6 |
| E/e′ ratio | 11.2 ± 4.1 |
| LA volume index, mL/m$^2$ | 29.9 ± 10.1 |
| EAT thickness, mm | 5.0 ± 1.8 |
| LVGLS, % | −21.1 ± 2.3 |
| LA reservoir strain, % | 30.6 ± 5.6 |
| LA conduit strain, % | 13.8 ± 5.0 |
| LA pump strain, % | 16.8 ± 4.7 |

Values are mean ± SD, *n* (percentage), or median (25–75th percentile).
A, late diastolic transmitral flow velocity; E, early diastolic transmitral flow velocity; e′, early diastolic mitral annular velocity; EAT, epicardial adipose tissue; eGFR, estimated glomerular filtration rate; GLS, global longitudinal strain; HDL, high density lipoprotein; LA, left atrium; LAD, left anterior descending artery; LCX, left circumflex artery; LDL, low density lipoprotein; LMT, left main trunk artery; LV, left ventricle; PCI, percutaneous coronary intervention; RAS, renin-angiotensin system; RCA, right coronary artery and TTE, transthoracic echocardiography.

**Table 2 Association of epicardial adipose tissue thickness with left ventricle/left atrium morphology and function in patients with chronic coronary syndrome**

| LV parameters | LV mass index, g/m$^2$ | | LVEF, % | | e′ velocity, cm/sec | | LVGLS, % | |
|---|---|---|---|---|---|---|---|---|
| | Sβ | *P*-value | Sβ | *P*-value | Sβ | *P*-value | Sβ | *P*-value |
| Univariable | 0.21 | <0.001 | 0.10 | 0.113 | −0.27 | <0.001 | −0.07 | 0.289 |
| Multivariable model 1 | 0.23 | <0.001 | 0.09 | 0.165 | −0.24 | <0.001 | −0.03 | 0.632 |
| Multivariable model 2 | 0.15 | 0.013 | 0.10 | 0.132 | −0.18 | 0.005 | −0.06 | 0.329 |
| **LA parameters** | **LA volume index, mL/m$^2$** | | **LA reservoir strain, %** | | **LA conduit strain, %** | | **LA pump strain, %** | |
| | Sβ | *P*-value | Sβ | *P*-value | Sβ | *P*-value | Sβ | *P*-value |
| Univariable | 0.21 | <0.001 | −0.13 | 0.041 | −0.20 | <0.001 | 0.07 | 0.282 |
| Multivariable model 1 | 0.19 | 0.001 | −0.11 | 0.065 | −0.19 | 0.002 | 0.06 | 0.302 |
| Multivariable model 2 | 0.12 | 0.055 | −0.07 | 0.261 | −0.13 | 0.037 | 0.06 | 0.411 |

Model 1 adjusted for age and sex. Model 2 adjusted for age, sex, hypertension, hyperlipidaemia, diabetes mellitus, body mass index, current smoking, and estimated glomerular filtration rate.
CCS, chronic coronary syndrome; e′, early diastolic mitral annular velocity; EAT, epicardial adipose tissue; EF, ejection fraction; GLS, global longitudinal strain; LA, left atrium; LV, left ventricle; Sβ, standardized beta.

conclusion, increased EAT thickness was independently associated with larger LV mass index, decreased e′, and impaired LA conduit function, but not with LV systolic parameters in CCS patients with prior PCI and normal LV systolic function.

## Lead author biography

Hikari Seki, MD, graduated from Fukushima Medical University in 2015. She is a Board-certified member of the Japanese Society of Internal Medicine, and she is a PhD student at the University of Tokyo. Her research interests include metabolic syndrome and deformation imaging.

## Authors' contributions

H.S., K.N., and K.H. contributed to the conception and design of the work. H.S., K.N., M.D., K.H., Y.Y., T.N., H.M., and I.K. contributed to the acquisition, analysis, or interpretation of data for the work. H.S. drafted the manuscript. K.N., M.D., K.H., Y.M., Y.Y., T.N., H.M., M.R.D.T., S.H., and I.K. critically revised the manuscript. All authors gave final approval and agreed to be accountable for all aspects of the work, ensuring integrity and accuracy.

## Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

## Funding

This work was supported in part by a Japan Heart Foundation Research Grant.

**Conflict of interest**: None declared.

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