Association of epicardial adipose tissue attenuation with coronary atherosclerosis in patients with a high risk of coronary artery disease

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HIGHLIGHTS

- Epicardial adipose tissue (EAT) attenuation and volume significantly correlated, but this relationship gradually diminished with increasing CAC scores
- EAT attenuation was associated with CAD risk factors and the presence of CAD and CAC.
- EAT attenuation was not associated with the presence of significant coronary lesions and triple-vessel plaques.
- EAT attenuation was associated with CAC score, SIS and SSS.

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ABSTRACT

Background and aims: Density may indicate some tissue characteristics and help reveal the role of epicardial adipose tissue (EAT) in coronary artery disease (CAD). Therefore, we assessed the association of EAT density with the coronary artery plaque burden in patients presenting with chest pain.

Methods: This retrospective cohort study comprised 614 patients (mean age 61 ± 9 years, 61% males) with a high cardiovascular disease risk, who underwent cardiac computed tomography angiography. Density was reflected as attenuation.

Results: EAT attenuation was significantly associated with EAT volume with a negative Pearson's correlation coefficient and gradually increased across coronary artery calcium (CAC) scores of 0, 1–100, 101–400 and > 400. EAT attenuation was tightly associated with CAD risk factors, including age, sex, BMI, total cholesterol, neutrophil to lymphocyte ratios and CAC score. The association between EAT attenuation and CAC score was strengthened after adjusting for multivariable indices (OR 1.21, 95% CI 1.05–1.40, $p = 0.01$) and further adjusting for EAT volume (OR 1.26 95% CI 1.06–1.51, $p < 0.01$). However, EAT attenuation was associated only with CAD presence (OR 1.32, 95% CI 1.02–1.69, $p < 0.05$), CAC presence (OR 1.28, 95% CI 1.02–1.60, $p < 0.05$), segment involvement score (OR 1.19, 95% CI 1.01–1.40, $p < 0.05$) and segment stenosis score (OR 1.19, 95% CI 1.01–1.40, $p < 0.05$) in the EAT volume- and multivariable-adjusted model. Additionally, EAT attenuation was not associated with significant coronary artery lesions and triple-vessel plaques.

Conclusions: Higher EAT attenuation is associated with a higher risk of CAD.

1. Introduction

Epicardial adipose tissue (EAT) surrounds the coronary arteries, directly connects to the arterial adventitia without fascia boundaries, has a unique transcriptome, and influences coronary artery biology via paracrine signaling [1,2]. EAT mainly exhibits a beige adipose phenotype, and its expansion via adipose cell hypertrophy and hyperplasia is associated with cardiovascular risk factors, coronary artery plaque burden, and coronary artery disease (CAD) prognosis [3–6].

As another important attribute of EAT, changes in attenuation may be more sensitive than volume in studying cardiovascular disease [7]. Measuring the attenuation may provide information on the potential

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biological changes, such as fibrosis and beige-white adipose transformation [8], in the EAT of CAD patients. Based on cardiac computed tomography angiography (CCTA) images, standard software can readily quantify the tissue density, as reflected by attenuation and expressed as Hounsfield units (HUs). The adipose tissue attenuation commonly ranges between −190 HU and −30 HU [9], and the exact quantification of EAT attenuation may help explain why EAT volume expansion alone is inconsistently associated with the presence and progression of CAD in many patients.

Thus far, the role of attenuation remains largely obscure. EAT attenuation is positively connected with coronary atherosclerosis [10]; however, others have found the inverse association in asymptomatic patients [11] and patients at high risk of cardiovascular disease [12]. EAT attenuation has even been shown to not correlate with coronary aortic calcium (CAC) levels [13] and may not be an independent risk factor in subjects with suspected acute coronary syndrome [14]. In addition, few studies have systematically addressed EAT attenuation in patients with different stages of cardiovascular disease. Therefore, we investigated the association of EAT attenuation and volume with the presence and severity of CAD in a large cohort of patients presenting with chest pain.

2. Patients and methods

2.1. Study population

A total of 812 consecutive inpatients (aged between 45 and 75 years) who underwent coronary calcium scoring (CCS) and a contrast-enhanced evaluation of coronary arteries by MDCT from July 2011 to December 2015 at Xiangya Hospital were recorded. Five of these patients had a history of prior open-heart surgery (including coronary artery bypass grafting and valve surgery), 20 patients had a history of prior percutaneous coronary intervention (PCI), 33 patients had malignancy, 7 patients had an indistinguishable pericardial sac, and 133 patients missed the covariate profile; these patients were all excluded. As a result, 614 subjects were involved in this study. All relevant medical records were collected. Patients were referred for evaluation by CCTA for clinical reasons with various indications, mainly including a low to intermediate pretest likelihood for the presence of CAD, perioperative risk assessment and atypical chest pain. This study was approved by the Ethics Committee of Xiangya Hospital, Central South University.

2.2. Risk indices

The BMI was calculated as weight (kg)/height (m) [2]. A positive family history of CAD was defined as evidence of myocardial infarction or cardiac death before the age of 60 years in at least one first-degree relative. Current smoking was defined as smoking ≥1 cigarette/day over the last year. Blood pressure was measured with a standard sphygmomanometer after 5 min of rest. Total cholesterol (TC), triglycerides (TG), high-density lipoprotein (HDL), low-density lipoprotein (LDL) and fasting glucose were measured using an automated analytical system (AU680; Beckman Coulter K.K., Lawrence, Kansas, USA). The atherogenic index of plasma (AIP) is defined as log (triglycerides/HDL), the NLR is the neutrophil to lymphocyte ratio, and the PLR is the platelet to lymphocyte ratio. Following the guidelines of the American Diabetes Association, diabetes mellitus type 2 (DM2) was diagnosed if one or more of the following criteria were met: a diagnostic history of diabetes and/or taking hypoglycemic drugs, HbA1c ≥ 6.5%, fasting glucose ≥126 mg/dL, or 2 h plasma glucose ≥200 mg/dL during an oral glucose tolerance test.

2.3. Computed tomography

The CCTA examination was performed with a dual-source CT (Somatom Definition, Siemens Healthcare, Forchheim, Germany) with a gantry rotation time of 270 ms, and the tube voltage for all the included subjects was 120 kV. For patients with a heart rate > 60 beats/min before the scan, an intravenous beta-blocker (metoprolol, 5–20 mg) was regularly administered. The Agatston score (AS) for coronary calcification was calculated based on a non-contrast-enhanced CT scan with a 3-mm slice thickness. Afterwards, a contrast agent was administered intravenously based on the patient's weight. EAT volume and attenuation were analyzed based on the contrast-enhanced CT scans.

2.4. Coronary artery assessment

1. Any CAD presence (Y/N): the presence of a plaque shown by CCTA, irrespective of stenosis.
2. CAC presence (Y/N): AS > 100.
3. Significant coronary artery lesion (Y/N): at least one lesion with stenosis of ≥50% of the vessel diameter.
4. Left main coronary artery (LMCA) plaque (Y/N): the presence of any plaque in the LMCA, irrespective of stenosis.
5. Triple-vessel plaques (Y/N): presence of a plaque in all three vessels (left anterior descending artery, left circumflex artery and right coronary artery), irrespective of stenosis.
6. The CAD severity was assessed by the segment involvement score (SIS) and segment stenosis score (SSS) [15]. A total of 16 segments were observed in the left main artery and the proximal, mid, and distal segments of the following 5 locations: (1) left anterior descending artery, (2) diagonal/intermediate branch, (3) left circumflex artery, (4) obtuse marginal branch, and (5) right coronary artery. Each individual coronary segment was graded 1 if it exhibited a plaque and 0 otherwise, irrespective of the degree of stenosis. The SIS was calculated as the sum for all 16 segments (range: 0 to 16). For each segment, the plaque severity was graded 0 if the stenosis was < 30% of the vessel diameter, 1 if the stenosis was ≥30% and < 50% of the vessel diameter, 2 if the stenosis was ≥50% and < 70% of the vessel diameter, and 3 if the stenosis was ≥70% of the vessel diameter. The SSS was calculated as the overall extent of coronary artery plaques (range: 0 to 48). Based on the SIS, the patients were classified into 7 classes as follows: 0 (n = 160, 26.1%), 1 (n = 107, 17.4%), 2 (n = 92, 15.0%), 3 (n = 86, 14.0%), 4 (n = 69, 11.2%), 5 (n = 44, 7.2%), and ≥6 (n = 56, 9.1%). Based on the SSS, the patients were classified into 10 classes as follows: 0 (n = 192, 31.3%), 1 (n = 58, 9.4%), 2 (n = 79, 12.9%), 3 (n = 62, 10.1%), 4 (n = 48, 7.8%), 5 (n = 44, 7.2%), 6 (n = 24, 3.9%), 7 (n = 22, 3.6%), 8 (n = 17, 2.8%), and ≥9 (n = 68, 11.1%). Segments with stenosis caused by a myocardial bridge were excluded from the SIS and SSS calculations.
7. Calcium scores were calculated using the Agatston method [16]. For the calcium scores, the patients were classified into 4 classes as follows: 0, 1 (1–100), 2 (101–400), and 3 (> 400). Of the patients, 40.1% (n = 246) were in class 0, 36.6% (n = 225) were in class 1, 14.5% (n = 89) were in class 2, and 8.8% (n = 54) were in class 3.

2.5. Analysis of EAT volume and attenuation

Adipose tissue volume and attenuation were derived from contrast-enhanced CCTA images. They were manually traced and calculated using the Mimics software (Materialise, Leuven, Belgium) [17]. We chose the lower surface of the left pulmonary artery origin as the superior border and the left ventricular apex as the inferior border. Because each coronal layer of the heart was significantly different, a thickness of approximately 3 mm was chosen when reconstructing the images to more accurately calculate the EAT volume and average attenuation. Thus, the images for each patient included approximately 30 slices. Each slice was traced along the pericardium, and three-dimensional volumetric quantification was used to measure the EAT volume.
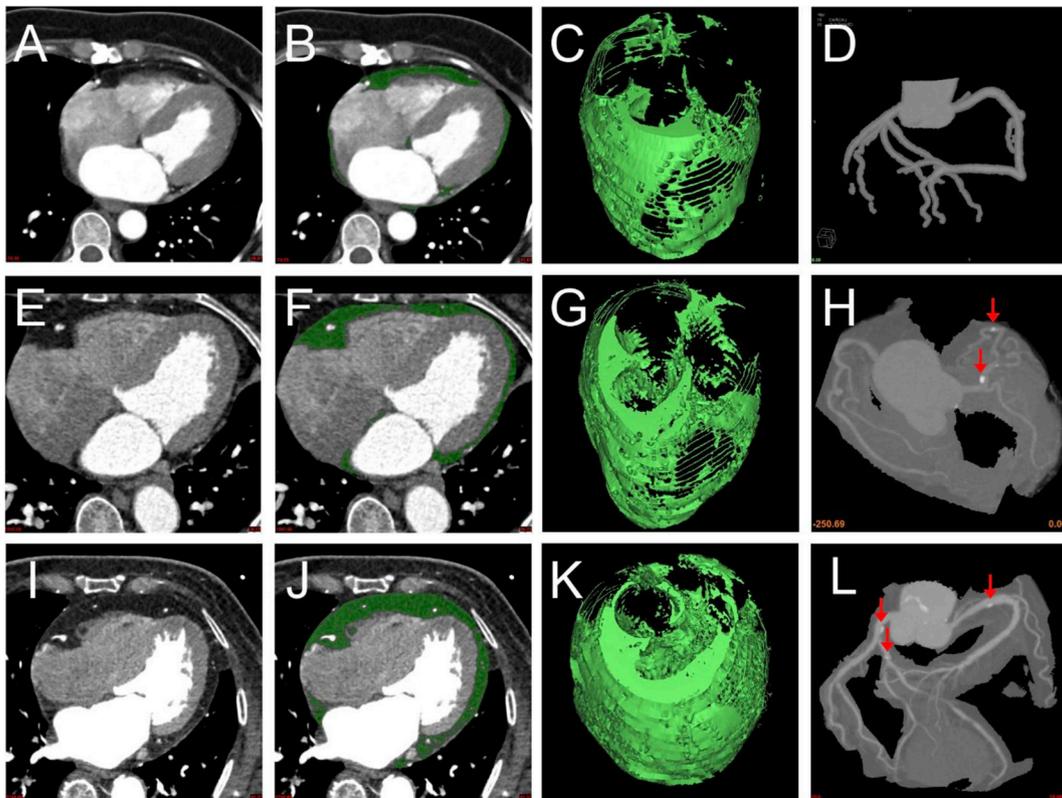
Fig. 1. EAT images from three representative patients.
(A), (E), (I) and (B), (F), (J) are CTA pictures before and after tracing; (C), (G), (K) are pictures of three-dimensional reconstructions of EAT with volumes of 60 cm^3, 103 cm^3, and 179 cm^3 as well as attenuation values of −73.98 HU, −78.36 HU, and −71.74 HU, respectively; (D), (H), (L) are images of the coronary artery tree with the CAC scores of 0, 109 and 163 (the dense white points marked by the red arrow are calcium plaques).

Attenuation was calculated as the mean HU value of all pixels from all slices. Values between −190 HU and −30 HU were considered to represent adipose tissue (see Fig. 1).

2.6. Reproducibility

To study the reproducibility of the EAT volume and attenuation measurements, scans for 20 randomly chosen subjects were independently measured by two persons who were blinded to the original measurements. The intraclass correlation (ICC) was 0.973 ($p < 0.001$) for EAT volume and 0.997 ($p < 0.001$) for EAT attenuation, showing excellent reproducibility.

2.7. Statistical analysis

The data analyses were conducted using IBM SPSS Statistics 22. For categorical variables, the numbers and percentages of subjects in each category are presented; for continuous variables, the mean ± standard deviation (SD) is presented. Pearson's correlation coefficients were used to assess the correlation between EAT attenuation and volume. Linear regression was used to analyze the association between CAD risk factors and EAT attenuation. Multivariate binary logistic regression was used to analyze the risk factors for the presence of any plaque, a significant coronary artery lesion, CAC, a LMCA plaque and triple-vessel plaques, and multivariate ordinal logistic regression was used to analyze the risk factors for CAD severity (CAC score, SIS, and SSS). Three multivariate models were used to evaluate the association of EAT volume/attenuation with CAD after adjusting for covariates as follows: (1) adjusted for age, sex and BMI; (2) adjusted for multivariable indices (age, sex, BMI, DM2, current smoking, SBP, TC, NLR, and statin use); and (3) adjusted for multivariable indices and EAT volume. A value of $p < 0.05$ was considered significant.

3. Results

3.1. Baseline characteristics of the patients

The baseline characteristics of the study cohort are depicted in Table 1. Overall, 614 hospitalized patients (mean age 61 ± 9 years, 61% males) were included in this study, of whom 74% had at least a plaque presence, 47% had a significant coronary artery lesion, 19% had an LMCA plaque, and 24% had triple-vessel plaques. Most of the patients suffered mild to moderate CAD according to their CAC score, SIS and SSS, as described above.

In the univariable logistic regression analysis, age, SBP, DM2, HDL, LDL, AIP, PLR, NLR, and EAT volume were significantly associated with any plaque presence in the overall population (Table 1).

3.2. Association between the EAT volume and attenuation

EAT attenuation was moderately and negatively correlated with the volume, with Pearson's correlation coefficients of −0.54 ($p < 0.001$) in the overall population, and −0.54 ($p < 0.001$) and −0.58 ($p < 0.001$) in individuals with and without any plaque, respectively. Pearson's correlation coefficients were −0.49 ($p < 0.001$) in subjects with a significant coronary artery lesion and −0.59 ($p < 0.001$) in those without.

Interestingly, Pearson's correlation coefficients between EAT attenuation and volume were −0.61 ($p < 0.001$), −0.57 ($p < 0.001$), −0.48 ($p < 0.001$), and −0.41 ($p = 0.002$) in patients with CAC scores of 0, 1–100, 101–400, and > 400, respectively, which suggests that the association between EAT attenuation and volume gradually weakened with the increase in the CAC score.

Table 1
Baseline clinical characteristics of 614 patients with chest pain.

	Overall	*p*-value
N	614	
Age (year)	61 ± 9	**< 0.001**
Male sex (%)	372 (61)	0.80
BMI (kg/m^2)	24.20 ± 3.14	0.06
Former smoking (%)	204 (33)	0.72
Current smoking (%)	133 (22)	0.59
Never smoking (%)	410 (67)	0.72
Systolic blood pressure (mmHg)	135 ± 19	**< 0.001**
Diastolic blood pressure (mmHg)	79 ± 11	0.29
DM2 (%)	276 (45)	**< 0.001**
CAD family history	38 (6)	0.14
Any CAD presence (%)	455 (74)	–
Triglycerides (mmol/L)	2.00 ± 1.90	0.12
Total cholesterol (mmol/L)	4.59 ± 1.07	0.05
HDL cholesterol (mmol/L)	1.15 ± 0.32	**< 0.01**
LDL cholesterol (mmol/L)	2.98 ± 0.95	**< 0.01**
AIP	0.16 ± 0.35	**< 0.05**
NLR	2.29 ± 1.46	**0.01**
PLR	114 ± 55	**< 0.01**
Statin use (%)	33 (5)	0.30
EAT volume (cm^3)	84 ± 37	**0.01**
EAT attenuation (HU)	−73.53 ± 5	0.27
CAC score (Agatston)	127 ± 330	–
Segment Involvement Score	2.4 ± 2.3	–
Segment Stenosis Score	3.6 ± 4.6	–
Significant coronary lesion (%)	289 (47)	–
Left main coronary artery plaque (%)	115 (19)	–
Triple-vessel plaques (%)	150 (24)	–

BMI, body mass index; DM2, diabetes mellitus type 2; CAD, coronary artery disease; HDL, high-density lipoprotein; LDL, low-density lipoprotein; AIP, atherogenic index of plasma; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; EAT, epicardial adipose tissue; CAC, coronary artery calcium.
$p < 0.05$ was regarded as indicating statistical significance, and significant *p*-values are in bold.

3.3. Association between CAD risk factors and EAT attenuation

In the age- and sex-adjusted model, EAT attenuation was negatively associated with the BMI, TC, AIP, and EAT volume and positively associated with the male sex, NLR, and CAC score. After further adjusting for the EAT volume, the negative association between AIP and EAT attenuation disappeared, and an association between age and attenuation was gained; the remaining associations were weakened but remained significant (Table 2).

3.4. EAT is associated with the presence of CAD and CAC

EAT attenuation was associated with a CAD presence (OR 1.32, 95% CI 1.02–1.69, $p < 0.05$) and a CAC presence (OR 1.28, 95% CI 1.02–1.60, $p < 0.05$) only in the multivariable- and EAT volume-adjusted model (Table 3). No significant association was observed between EAT attenuation and the presence of a significant coronary artery lesion or triple-vessel plaques.

3.5. EAT is associated with CAD plaque severity

The association between the EAT volume/attenuation and CAD severity was analyzed. Three indices were introduced to obtain a comprehensive assessment of the extent of CAD [the SIS, SSS and CAC score (Agatston score)]. EAT attenuation was significantly associated with the CAC score, and the association was strengthened after adjusting for multivariable indices and further strengthened when adjusting for EAT volume. EAT attenuation was associated with the SIS and SSS only after adjusting for EAT volume with adjustment for other risk factors (Table 4).

4. Discussion

In this clinical study, we examined the association of EAT attenuation derived from CTA scans with both the CAD presence, as assessed by the plaque presence, and the CAD severity, as assessed by the SIS, SSS, and CAC score. The SIS and SSS better reflected the degree of coronary artery stenosis [15], while higher CAC scores were strongly associated with a poor prognosis of CAD [18]. We found that EAT attenuation was moderately and negatively associated with EAT volume and that this association was gradually and apparently weakened in patients with progressive CAD. EAT attenuation was associated with an adverse CAD risk factor profile. EAT attenuation was positively associated with the CAC score in all three models; the association was enhanced after further adjusting for EAT volume but was present for only the SIS and SSS in the EAT volume- and multivariable-adjusted model. The association of EAT attenuation with CAD/CAC presence was similar to that of the SIS or SSS in the models. These findings suggest that EAT attenuation could be an important attribute of EAT that could help define the role of EAT in CAD development.

Large studies have reported that an increased EAT volume promotes early development of atherosclerosis [19] and is positively associated with the CAC score and an adverse CAD prognosis [20]. Additionally, this measure is linked to severe coronary stenosis in patients with non-calcified and partially calcified plaques [21]. The mechanism underlying these associations may be linked to a disordered secretory profile of EAT [22], with substantial accumulation of inflammation-related factors, and by mediators that are secreted by infiltrating macrophages [23,24]. The accumulated inflammatory factors could easily induce and aggravate the interstitial fibrosis in adipose tissue, which is one of the most important driving factors and a hallmark of the metabolic dysfunction of adipose tissue [25].

Adipose tissue fibrosis alone increases its attenuation because of the excess accumulation and deposition of extracellular matrix [26], while adipose tissue expansion often results in a decrease in attenuation [27]. The latter is mainly caused by adipose cell hypertrophy and hyperplasia and is attributed to the accumulation of too many lipid droplets, which decreases adipose tissue density and shows lower fat attenuation [28]. With CAC progression, the association between EAT attenuation and volume was gradually weakened in our study, and the lower correlation in severe CAD patients is consistent with the previous finding [29]. Our results indicated that unsynchronized changes existed between the two EAT attributes during CAC progression. Expansion and fibrosis exist simultaneously in EAT, and the former would aggravate the fibrosis due to the hypoxic environment caused by the inability of the neovasculature to keep pace with fast adipose tissue expansion [30]. Fibrosis of the fat tissue would alleviate or reverse the decrease in the fat attenuation, leading to a gradually weakened association, which would account for the unsynchronized EAT volume and attenuation changes during disease progression.

Fibrosis in fat tissue is tightly associated with inflammation [31], and this association is mainly attributed to the accumulation of inflammation-related factors and mediators that promote enhanced extracellular matrix synthesis and excess collagen deposition in fat tissue. The NLR, which represents a systemic inflammatory condition, is positively associated with CAD [32] and was tightly associated with EAT attenuation in this study. The positive association between EAT attenuation and the NLR in our study suggests that EAT attenuation may be indirectly influenced by the low-grade inflammatory state, which will further induce adipose tissue remodeling and fibrosis [30,33] and consequently increase the fat attenuation. Thus, the positive association between EAT attenuation and the CAC score may be attributed to this inflammatory state and consequent fibrosis.

Our positive result was supported by the findings of other studies. For instance, one study reported that EAT attenuation is associated with the CAC score with a positive Pearson's correlation coefficient [13], and other studies found that increased EAT attenuation is positively

Table 2

Relation between CAD risk factors and EAT attenuation.

	EAT attenuation (HU), beta (95%)			
	Age and sex adjusted	*p*-value	Age, sex and EAT volume adjusted	*p*-value
	Beta (95% CI)		Beta (95% CI)	
Age	0.03 (−0.02 to 0.08)	0.29	0.08 (0.04–0.12)	**< 0.001**
Male sex	1.57 (0.68–2.45)	**< 0.001**	1.96 (1.22–2.69)	**< 0.001**
BMI	−0.25 (−0.39 to −0.12)	**< 0.001**	0.17 (0.05–0.30)	**< 0.01**
Current smoking	−0.58 (−1.69 to 0.54)	0.31	0.01 (−0.91 to 0.94)	0.99
Systolic blood pressure	−0.02 (−0.04 to 0.01)	0.13	−0.01 (−0.03 to 0.01)	0.32
Triglycerides	−0.17 (−0.39 to 0.05)	0.14	−0.07 (−0.26 to 0.11)	0.43
Total cholesterol	−0.43 (−0.83 to −0.04)	**< 0.05**	−0.38 (−0.71 to −0.06)	**< 0.05**
HDL	0.02 (−1.35 to 1.40)	0.98	−0.67 (−1.81 to 0.47)	0.25
LDL	−0.36 (−0.80 to 0.08)	0.11	−0.29 (−0.66 to 0.07)	0.11
AIP	−1.61 (-2.86 to −0.35)	**< 0.05**	−0.40 (-1.46 to 0.66)	0.46
NLR	0.31 (0.02–0.60)	**< 0.05**	0.25 (0.01–0.49)	**< 0.05**
PLR	0.01 (0.00–0.01)	0.11	0.00 (0.00–0.01)	0.48
DM2 (yes)	−0.62 (−1.46 to 0.22)	0.15	−0.11 (−0.80 to 0.59)	0.77
CAC score	0.002 (0.001–0.003)	**< 0.01**	0.002 (0.000–0.003)	**< 0.01**
EAT volume	−0.08 (−0.09 to −0.07)	**< 0.001**	−0.08 (−0.09 to −0.07)	**< 0.001**

CAD, coronary artery disease; EAT, epicardial adipose tissue; BMI, body mass index; HDL, high-density lipoprotein; LDL, low-density lipoprotein; AIP, atherogenic index of plasma; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; DM2, diabetes mellitus type 2; CAC, coronary artery calcium; CI, confidence interval.
$p < 0.05$ was regarded as indicating statistical significance, and significant *p*-values are in bold.

associated with coronary atherosclerosis [10] and even with myocardial infarction [34]. However, other groups have reported the opposite observation and showed that decreased attenuation was associated with an impaired CAD profile [11,12,35]. Because EAT attenuation was positively associated with both the NLR and CAC score in this study, the divergent associations between attenuation and CAD may be caused by the inclusion of patients in different studies experiencing different degrees of inflammation and fibrosis in the EAT. Interestingly, this divergent association is also present in studies of the association between attenuation of the visceral/subcutaneous adipose tissue and CAD disease [13,36].

In contrast, the influence of fibrosis on the fat attenuation is largely determined by the base fat volume, because a large volume is difficult to slow down or reverse, but a small amount of fibrosis may have a substantial impact on a small fat volume. The average BMI values and EAT volumes of the Chinese population in this study are far below those observed in studies of European [12] and American populations [11], which show negative associations. Thus, our population may be more easily influenced by the low-grade inflammatory state, resulting in a positive association. Additionally, the potential activation of beige adipose cells may also increase attenuation due to the abundant vascularity, mitochondria and the decrease in the lipid content [37].

Thus, the association between EAT attenuation and CAD mainly depends on the influence of the EAT volume and fibrosis. In studies of the relationship between EAT attenuation and CAD, the EAT volume and inflammation should be considered; in this circumstance, changes in EAT attenuation may provide complementary information during CAD development and progression.

4.1. Study limitations

Our study used a retrospective, single-center research design, and we did not measure the waist or hip circumference; instead, we investigated the BMI. Second, we did not include outpatients, and numerous patients were excluded due to insufficient data, which could have led to selection bias. Additionally, causal relationships could not be inferred from our study due to the retrospective nature of the design. We excluded patients with a prior history of heart surgery and PCI because surgical intervention may change the EAT anatomical structure in the former and because the stenosis caused by plaques was changed

Table 3

The association of EAT attenuation with the presence of CAD, significant coronary lesion, CAC and triple-vessel plaques.

		EAT attenuation	
		OR (95% CI)	*p*-value
CAD presence	Age, gender, BMI adjusted	1.14 (0.95–1.38)	0.16
	Multivariable adjusted[a]	1.15 (0.95–1.41)	0.16
	Multivariable + EAT adjusted	1.32 (1.02–1.69)	**< 0.05**
Significant coronary lesion presence	Age, gender, BMI adjusted	1.00 (0.86–1.17)	0.98
	Multivariable adjusted[a]	1.01 (0.85–1.19)	0.93
	Multivariable + EAT adjusted	1.04 (0.85–1.26)	0.72
CAC presence	Age, gender, BMI adjusted	1.16 (0.97–1.40)	0.11
	Multivariable adjusted[a]	1.20 (0.99–1.45)	0.06
	Multivariable + EAT adjusted	1.28 (1.02–1.60)	**< 0.05**
Triple-vessel plaques presence	Age, gender, BMI adjusted	1.10 (0.92–1.31)	0.31
	Multivariable adjusted[a]	1.13 (0.94–1.36)	0.18
	Multivariable + EAT adjusted	1.10 (0.89–1.37)	0.37

CAD, coronary artery disease; EAT, epicardial adipose tissue; CAC, coronary artery calcium; CI, confidence interval
Odds ratios (ORs) are depicted per 5-HU increase of EAT attenuation; $p < 0.05$ was regarded as indicating statistical significance, and significant *p*-values are in bold.

[a] Including age, sex, BMI, diabetes mellitus type 2, current smoking, systolic blood pressure, total cholesterol, neutrophil to lymphocyte ratio, and statin use.

Table 4
The association of EAT attenuation with CAC score, SIS and SSS.

		EAT attenuation	
		OR (95% CI)	*p*-value
CAC score	Age, gender, BMI adjusted	1.16 (1.01–1.34)	< 0.05
	Multivariable adjusted[a]	1.21 (1.05–1.40)	**0.01**
	Multivariable + EAT adjusted	1.26 (1.06–1.51)	**< 0.01**
SIS	Age, gender, BMI adjusted	1.10 (0.96–1.26)	0.18
	Multivariable adjusted[a]	1.14 (1.00–1.31)	0.06
	Multivariable + EAT adjusted	1.19 (1.01–1.40)	**< 0.05**
SSS	Age, gender, BMI adjusted	1.07 (0.94–1.23)	0.32
	Multivariable adjusted[a]	1.13 (0.99–1.30)	0.09
	Multivariable + EAT adjusted	1.19 (1.01–1.40)	**< 0.05**

EAT, epicardial adipose tissue; CAD, coronary artery disease; CAC, coronary artery calcium; SIS, Segment Involvement Score; SSS, Segment Stenosis Score; CI, confidence interval.
Odds ratios (ORs) are depicted per 5-HU increase of EAT attenuation; $p < 0.05$ was regarded as indicating statistical significance, and significant *p*-values are in bold.

[a] Including age, sex, BMI, diabetes mellitus type 2, current smoking, systolic blood pressure, total cholesterol, neutrophil to lymphocyte ratio, and statin use.

in the latter; thus, neither group of patients was appropriate for this study. The mechanism of EAT attenuation and CAD still need further investigation. This study was conducted in Chinese population, and the results may differ for other ethnic groups.

4.2. Conclusions

The association between EAT attenuation and CAD was largely influenced by the different stage and severity of CAD and may be mainly determined by the degree of fibrosis in fat tissue and the base EAT volume. EAT attenuation may reveal composition changes in adipose tissue during disease progression and function as a valuable complementary biomarker in unveiling the role of EAT in CAD, especially when the EAT volume and fibrosis are considered.

Conflicts of interest

The author(s) declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Author contributions

ZH.L. contributed to the conception and design of the study; the acquisition, analysis and interpretation of the data and the drafting of the manuscript. SJ.W., YQ.W., NB.Z., J.S. and M.J. contributed to the acquisition of the data and the drafting of the manuscript. C.S. contributed to the conception and design of the study and critical revision of the manuscript for important intellectual content. FY.L. contributed to the conception and design of the study, the analysis and interpretation of the data and critical revision of the manuscript for important intellectual content. All authors approved the final version of the manuscript for publication.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.atherosclerosis.2019.01.033

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