



Correlation between clinical characteristics and epicardial adipose tissue features in acute myocarditis patients using coronary computed tomography (CT) vascular imaging: a case-control study with retrospective data collection

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Background: Epicardial adipose tissue (EAT) is unique type of visceral adipose tissue, sharing the same microcirculation with myocardium. This study aimed to assess the imaging features of EAT in patients with acute myocarditis (AM) and explore the relationships with clinical characteristics.

Methods: For this retrospective case-control study, totally 38 AM patients and 52 controls were screened retrospectively from January 2019 to December 2022, and the EAT volume was measured from coronary computed tomography (CT) angiography imaging. Histogram analysis was performed to calculate parameters like the mean, standard deviation, interquartile range and percentiles of EAT attenuation. Whether EAT features change was assessed when clinical characteristics including symptoms, T wave abnormalities, pericardial effusion (PE), impairment of systolic function, and the need for intensive care presented.

Results: The EAT volume (75.2±22.8 mL) and mean EAT attenuation [-75.8±4.4 Hounsfield units (HU)] of the AM group was significantly larger than the control group (64.7±26.0 mL, $P=0.049$; -77.9±5.0 HU, $P=0.044$). Among the clinical characteristics, only the presence of PE was associated with changes in EAT features. Patients with PE showed significantly changes in EAT attenuation including mean attenuation [analysis of variance (ANOVA) $P=0.001$] and quantitative histogram parameters. The mean attenuation of patients with PE (-71.9±4.0 HU) was significantly larger than controls (-77.9±5.0 HU, Bonferroni corrected $P<0.001$) and patients without PE (-77.4±3.5 HU, Bonferroni corrected $P=0.003$). Observed in histogram, the overall increase in EAT attenuation could lead to decrease in EAT volume, which resulted in no statistically significant difference in EAT volume between the AM patients with PE and controls (64.7±26.0 vs. 72.2±28.3 mL, Bonferroni corrected $P>0.99$).

Conclusions: Compared to controls, EAT volume was significantly larger in AM, and EAT attenuation

increased notably in the presence of PE. We recommend evaluating EAT volume and attenuation simultaneously when quantifying EAT using CT attenuation thresholds.

Keywords: Computed tomography (CT); histogram; epicardial fat; myocarditis; pericardial effusion (PE)

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Introduction

Myocarditis is an inflammatory disease of the myocardium, mostly caused by viral infection, resulting in inflammatory infiltrates within the myocardium (1). It has been established that adipokines secreted by adipose tissue, which can be either pro-inflammatory or anti-inflammatory, play a role in linking obesity to various cardiovascular diseases, including myocarditis and inflammatory cardiomyopathy (2-4). For instance, adiponectin protects the heart from acute viral infection and subsequent pathological cardiac remodeling (5,6). Epicardial adipose tissue (EAT) is a unique type of visceral adipose tissue without distinct boundaries, sharing the same microcirculation with myocardium (7). And it also serves as a source of adipokines that have an impact on both coronary vessels and the myocardium (8). Nevertheless, there has been limited research into the imaging characteristics of EAT in patients with acute myocarditis (AM).

Volume (EAT-Vol) and attenuation (EAT-At) of EAT, as measured on computed tomography (CT) scans, serve as biomarkers for cardiometabolic diseases, including but not limited to type 2 diabetes mellitus, coronary artery disease (CAD), heart failure, and atrial fibrillation (9-13). These parameters provide insights into both the quantity and composition of EAT. Due to the intimate anatomical and functional connection between EAT and the myocardium, as mentioned earlier, our hypothesis was that EAT characteristics derived from cardiac CT imaging in patients with AM would exhibit abnormalities when compared with those of the control group. This study aimed to assess the distinctions in imaging features of EAT between AM and control groups. Furthermore, we examined the correlation between clinical characteristics and EAT features in AM patients, which would have the potential to provide new imaging markers for the diagnosis and prognostic evaluation of myocarditis. Taking into account that attenuation of EAT is associated with fat composition (14) and recognizing the non-uniform nature of this composition, we conducted histogram analysis of EAT-At to obtain quantitative

parameters for all participants. This analysis helps us gain a better understanding of the distribution and characteristics of fat within the EAT, providing valuable insights into its composition and potential relevance to AM. We present this article in accordance with the STROBE reporting checklist (available at <https://qims.amegroups.com/article/view/10.21037/qims-23-1407/rc>).

Methods

Population and design

This is a single-center retrospective case-control study. We screened 156 consecutive adult patients admitted to the hospital for new-onset symptoms and clinically suspected myocarditis from January 2019 to December 2022. Complete baseline blood examinations for cardiac biomarkers (T-troponin, N-terminal pro-B-type natriuretic peptide) and inflammatory indexes, continuous 12-lead electrocardiography (ECG) telemonitoring, transthoracic color Doppler echocardiogram and cardiac magnetic resonance (CMR) were collected from all of the patients. To diagnose AM, we referred to the algorithm of the European Society of Cardiology guidelines (1). Clinically suspected AM was diagnosed when symptomatic patients with chest pain fulfilled one or more diagnostic criteria (new ECG modification, elevated troponin, wall motion abnormalities with preserved left ventricular ejection fractions at echocardiography) or when asymptomatic patients had two or more diagnostic criteria. Clinical history, physical examination, and laboratory results were further analyzed, and those with CAD, systemic immune-mediated or toxic myocarditis were excluded. A definite diagnosis of AM was made in the event of two or more CMR Lake Louise criteria (myocardial edema, hyperemia, and late gadolinium enhancement (LGE) or pathologically diagnosed with AM after endomyocardial biopsy (EMB) (1). Characterizations of AM, including the common symptoms of chest pain and fever, ST-segment and T-wave (ST/T) changes,

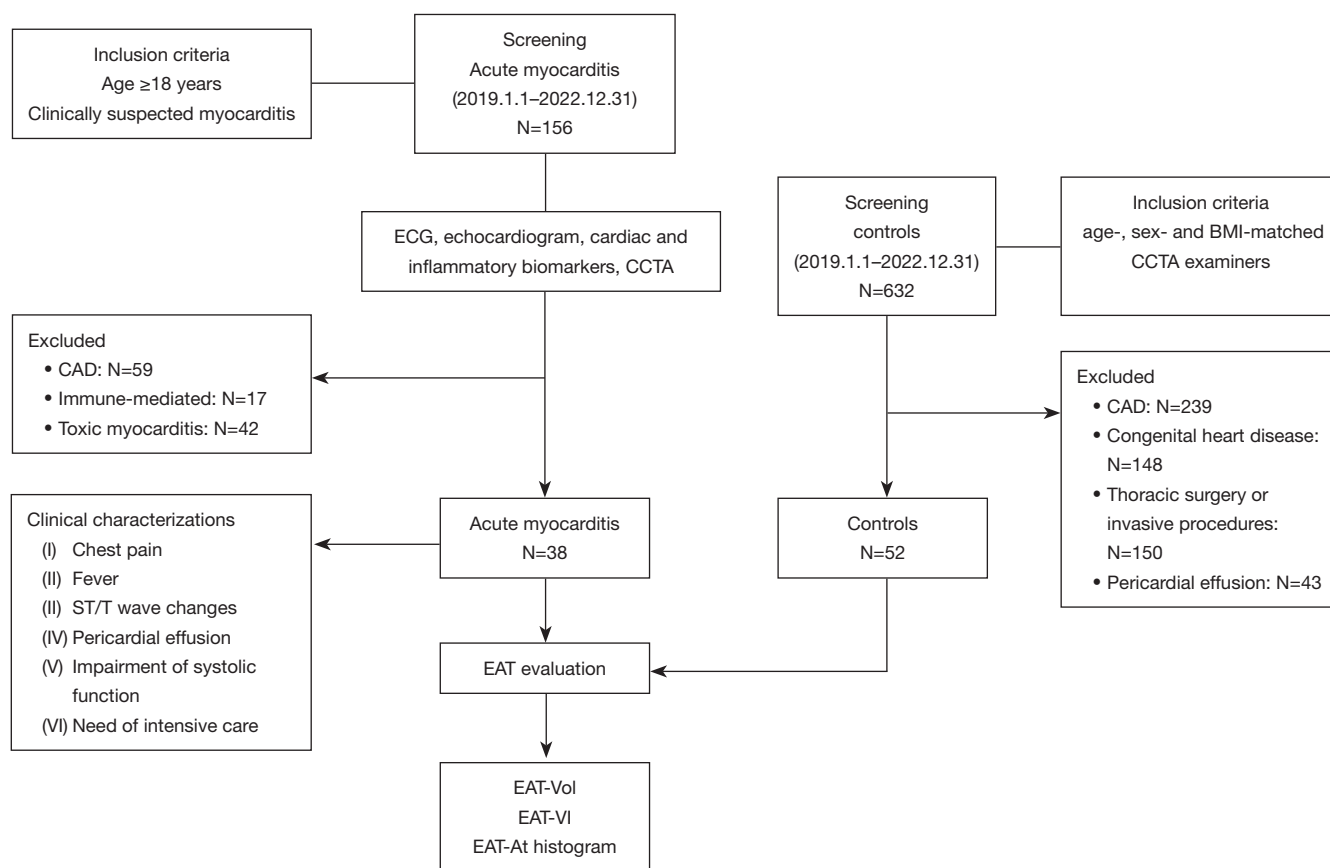


Figure 1 Flow chart indicating the derivation of the study population. ECG, electrocardiography; CCTA, coronary computed tomography angiography; CAD, coronary artery disease; ST/T, ST-segment and T-wave; BMI, body mass index; EAT, epicardial adipose tissue; EAT-Vol, epicardial adipose tissue volume; EAT-VI, epicardial adipose tissue volume index; EAT-At, epicardial adipose tissue attenuation.

pericardial effusion (PE), impairment of systolic function, and the need for intensive care during hospitalization, were recorded. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by ethics board of Zhongshan Hospital of Fudan University (No. B2020-088R) and informed consent was taken from all the patients.

A control group consisted of age-, sex- and body mass index (BMI)-matched participants who were selected from all subjects who underwent coronary CT angiography (CCTA) for health check-ups in our center with the same CT scanner from January 2017 to August 2020. The detailed inclusion criteria were as follows: (I) Negative coronary vessels observed from CCTA; (II) normal morphology and size of the heart; (III) no history of surgery or invasive procedures involving the lung, mediastinum or heart; and (IV) absence of PE and marked pericardial thickening (>5 mm).

The study proceeded in two main steps. First, EAT imaging measurements were compared between the AM group and the control group. In the second step, the AM group was further stratified into subgroups based on the presence or absence of the six clinical features. Subsequently, EAT-Vol and EAT-At were compared within these six pairs of subgroups. If any clinical features were determined to have a significant association with changes in EAT, then the corresponding subgroups were also compared with the control group for further analysis. An overview of this study is presented in the form of a flow chart, as depicted in *Figure 1*.

Scan protocol and image reconstruction

All the CCTA scans were performed on the same CT scanner (Aquilion ONE; Toshiba Medical Systems Corporation, Japan) with 320 detector rows. Patients

with heart rate >65 beats/min took metoprolol orally approximately 1–1.5 hours before CCTA examination. Sublingual nitroglycerine (0.5 mg) was administered 5 min before scanning, except in the case of contraindications. Intravenous injection of iodinated contrast medium was injected through the right cubital vein with a double-cylinder high-pressure syringe (370 mgI/mL, flow rate 4.0–5.0 mL/s, total amount of injection 0.8 mL/kg) followed by saline (25 mL) injection at the same flow rate. The scanning parameters were as follows: tube voltage 120 kV, current automatically adapted to the patient's BMI and thoracic anatomy, z-coverage 120–160 mm.

Quantification of EAT

All the images were imported from picture archiving and communication system (PACS) to the postprocessing workstation (uWS-CT, R004, Shanghai United Imaging Healthcare, China). EAT was defined as the visceral fat between the surface of the myocardium and the visceral layer of the pericardium. The pericardium itself was delineated manually, starting from the bifurcation of the pulmonary trunk and extending to the end of the pericardial sac. To ensure measurement consistency, this step was performed by a radiologist (C.Y.) with 8 years of experience. A volume of interest (VOI) encompassing the entire heart was established, and a frequency distribution table of CT attenuation unit value within the VOI was extracted and then exported to a personal computer. To identify fat-containing voxels, a threshold ranging from –190 to –30 Hounsfield units (HU) was applied. The EAT-Vol was calculated as the product of the voxel volume and the count of fat-containing voxels. To account for variations in heart size among individuals and mitigate errors arising from these differences, the volume index of EAT volume (EAT-VI) was defined as the ratio of EAT-Vol to heart volume (Heart-V). The Heart-V equaled the difference between the volume of heart VOI and EAT-Vol.

Histogram analysis of EAT

The histogram analysis of EAT was performed in SPSS v. 19.0.0 software (SPSS, Inc., Chicago, Illinois, USA) using the frequency distribution table which mentioned in the previous step. The frequency distribution data within the interval of (–190, –30 HU) which represented EAT being extracted and imported into the SPSS software for histogram analysis and the following parameters were

obtained: mean value (EAT-At-mean), standard deviation (EAT-At-SD), interquartile range (EAT-At-IQR), 5th-percentile value (EAT-At5%), 10th-percentile value (EAT-At10%), 25th-percentile value (EAT-At25%), 75th-percentile value (EAT-At75%), 90th-percentile value (EAT-At90%), 95th-percentile value (EAT-At95%) of the EAT attenuation (*Figure 2*).

Statistical analysis

Statistical analyses were performed with SPSS v. 19.0.0 software (SPSS, Inc., Chicago, Illinois, USA). Normally distributed variables were presented as mean \pm SD. Nonnormally distributed variables were presented as median (25th–75th percentile). Comparisons of characteristics between different groups of patients were performed using the *t*-test for two groups. Nonnormally distributed continuous variables were compared between patient subgroups using the Mann-Whitney *U*-test. Categorical variables were compared using the Chi-squared test and $P < 0.05$ (two-sided) was considered indicative of a statistically significant difference. If differences exist, further subdivide the subjects into subgroups based on clinical characteristics and the analysis of variance (ANOVA) test with post-hoc Bonferroni correction was applied.

Results

General characteristics of the enrolled participants

As presented in *Table 1*, a total of 38 patients with AM and 52 control subjects were included in this study (*Table 1*). Within the AM group, 22 patients (58%) reported experiencing chest pain, and 17 (45%) had fever during the onset of disease. The other symptoms included cough, dyspnea, fatigue, diarrhea, and abdominal pain. ECG findings indicated ST/T changes, including ST-segment elevation or depression and T-wave inversions, presented in 27 (71%) AM patients. All patients underwent echocardiography, revealing regional left ventricular and/or right ventricular dysfunction in 11 (29%) patients, while PE was observed in 11 (29%) patients. During hospitalization, 21 (55%) patients required intensive care, among which one female patient died during hospitalization.

Comparison of EAT measurements between the AM and control groups

The comparison of EAT measurements between the AM

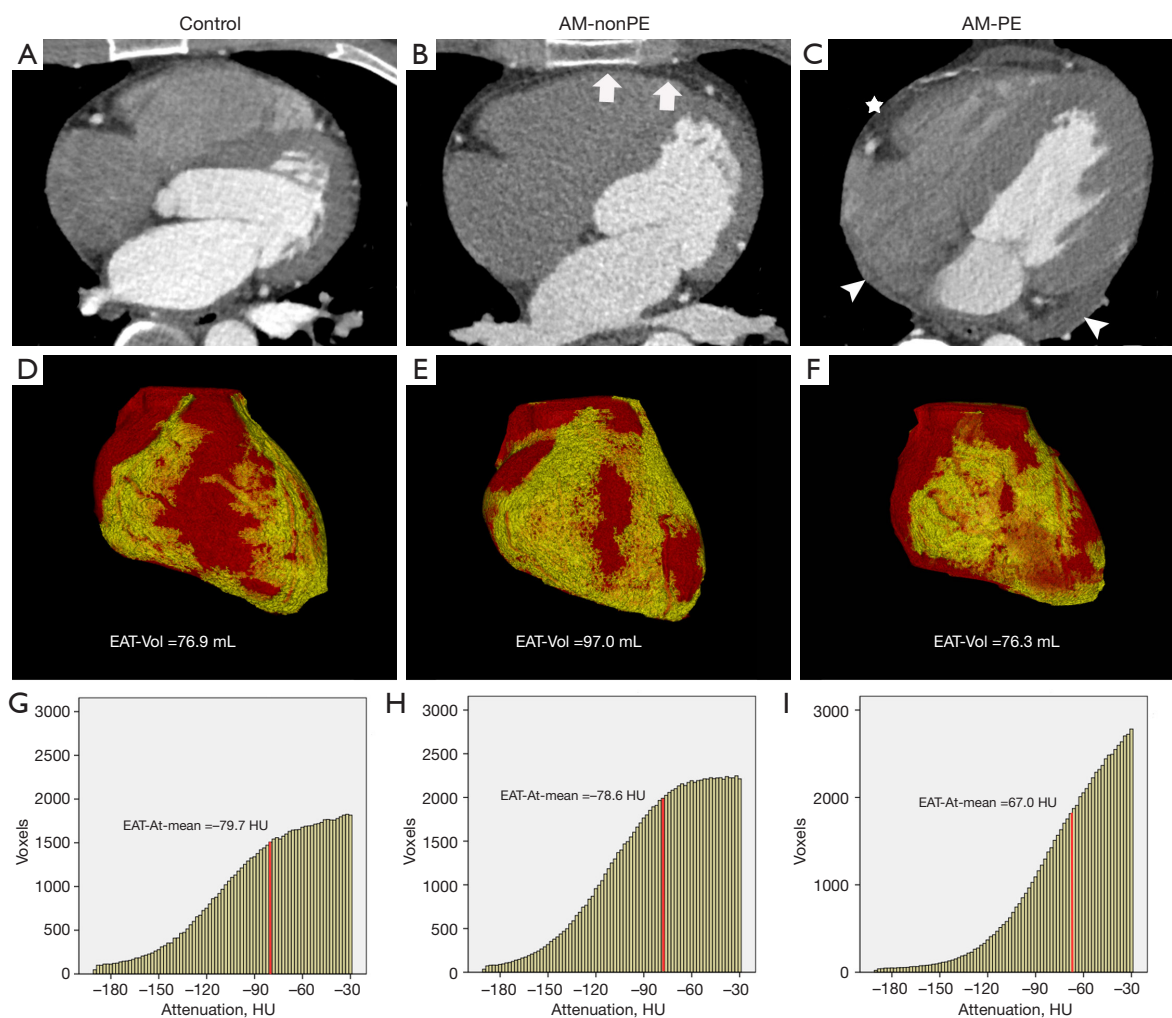


Figure 2 The EAT volume and attenuation could be visualized in VR and Histogram. Examples of EAT visualization in control (A,D,G), patients of acute myocarditis without pericardial effusion (B,E,H) and with pericardial effusion (C,F,I). Axis image reveals increased thickness of EAT in the precordial region (B, white arrows) and VR demonstrates more prominent presence of EAT I in acute myocarditis patients. EAT around the right coronary artery showing higher attenuation (C, asterisk) in acute myocarditis patients with pericardial effusion (C, arrowheads). Histogram (G-I) displays the volume of each Hounsfield unit predefined as fat during -190 to -30 HU. The red line indicates the value of mean EAT attenuation. AM-PE, acute myocarditis with pericardial effusion; AM-nonPE, acute myocarditis without pericardial effusion; EAT-Vol, epicardial adipose tissue volume; EAT-At, epicardial adipose tissue attenuation; HU, Hounsfield units; EAT, epicardial adipose tissue; VR, volume rendering.

and control groups revealed the following findings. The EAT-Vol of the AM group was 75.2 ± 22.8 mL, which was significantly larger than that of the control group (64.7 ± 26.0 mL, $P=0.049$). Moreover, the EAT-VI remained significantly different between the two groups even when normalized to the volume of the heart (AM *vs.* control: 0.09 ± 0.03 *vs.* 0.11 ± 0.04 , $P=0.032$). Regarding EAT-At, the mean EAT-At value in the AM group was -75.8 ± 4.4 HU, which was significantly higher than that

in the control group (-77.9 ± 5.0 HU, $P=0.044$). Further histogram analysis revealed that this change was primarily driven by the increase in EAT-At75% (-49.6 ± 3.0 *vs.* -51.2 ± 3.8 HU, $P=0.033 < 0.05$) and EAT-At90% (-37.4 ± 1.4 *vs.* -38.2 ± 1.7 HU, $P=0.019$) in the AM group (Table 1). Through histogram analysis, it was observed that the histogram curves of EAT for all subjects exhibited a pattern of lower values on the left side and higher values on the right side (Figure 2G-2I).

Table 1 Comparison of demographic and EAT features of the AM patients and control groups

Characteristics	Control group (N=52)	AM group (N=38)	P value
Male	34 [65]	29 [76]	0.215
Age (years)	31.8±6.8	31.5±9.9	0.871
BMI (kg/m ²)	24.3±3.6	24.8±3.2	0.510
Clinical characteristics			
Chest pain	–	22 [58]	–
Fever	–	17 [45]	–
T wave abnormalities	–	27 [71]	–
Impaired systolic function	–	11 [29]	–
Pericardial effusion	–	11 [29]	–
Critical illness	–	21 [55]	–
EAT features			
Heart-V (mL)	703.5±123.3	730.8±141.6	0.332 [#]
EAT-VI	0.11±0.04	0.09±0.03	0.032*
EAT-Vol (mL)	64.7±26.0	75.2±22.8	0.049*
EAT-At-mean (HU)	–77.9±5.0	–75.8±4.4	0.044*
EAT-At-SD (HU)	33.1±2.4	32.4±2.1	0.179
EAT-At-IQR (HU)	47.6±4.6	46.7±3.9	0.309
EAT-At 5% (HU)	–139.7±8.7	–136.6±7.8	0.077
EAT-At 10% (HU)	–123.4±8.7	–120.7±7.5	0.114
EAT-At 25% (HU)	–98.8±7.5	–96.3±6.5	0.091
EAT-At 50% (HU)	–73.2±6.2	–70.9±5.1	0.064
EAT-At 75% (HU)	–51.2±3.8	–49.6±3.0	0.033*
EAT-At 90% (HU)	–38.2±1.7	–37.4±1.4	0.019*
EAT-At 95% (HU)	–33.8±0.8	–33.5±0.8	0.111

Data are shown as mean ± SD or number [%]. [#], Mann-Whitney U-test, while *t*-tests were utilized for intergroup comparisons of other quantitative data; *, significance of P value (P<0.05). T wave abnormalities include ST-segment elevation or depression, T-wave inversions. EAT, epicardial adipose tissue; AM, acute myocarditis; BMI, body mass index; EAT-VI, epicardial adipose tissue volume index; EAT-Vol, epicardial adipose tissue volume; EAT-At, epicardial adipose tissue attenuation; HU, Hounsfield units; EAT-At-SD, standard deviation of EAT-At; EAT-At-IQR, interquartile range of EAT-At; SD, standard deviation.

EAT evaluation based on patient characteristics

The mean EAT-At of the AM with PE (AM-PE) subgroup (–71.9±4.0 HU) was significantly higher than that in the AM without PE (AM-nonPE) subgroup (–77.4±3.5 HU, P<0.001). This indicates a significant increase in EAT-At when PE was present. The EAT-Vol was not significantly different between the two subgroups (AM-PE *vs.* AM-

nonPE: 72.2±28.3 *vs.* 76.4±20.6 mL, P=0.613), even after normalizing to the volume of the heart, as indicated by EAT-VI (0.10±0.04 *vs.* 0.11±0.03, P=0.584). There were no significant differences observed in EAT-At, EAT-Vol or EAT-VI between AM patients with and without chest pain, fever, ST/T changes, impairment of systolic function or the need for intensive care during hospitalization (*Table 2*).

Table 2 EAT evaluation based on patient characteristics

Clinical characteristics	EAT features	With	Without	P value
Chest pain	EAT-Vol (mL)	76.0±19.6	73.9±27.3	0.783
	EAT-At-mean (HU)	-76.7±3.5	-74.6±5.2	0.149
	EAT-VI	0.11±0.03	0.11±0.05	0.917
Fever	EAT-Vol (mL)	79.3±28.3	71.8±17.1	0.322
	EAT-At-mean (HU)	-75.4±5.8	-76.2±2.9	0.591
	EAT-VI	0.11±0.04	0.10±0.03	0.621
ST/T changes	EAT-Vol (mL)	72.2±21.5	82.4±25.2	0.217
	EAT-At-mean (HU)	-75.6±4.5	-76.4±4.1	0.620
	EAT-VI	0.10±0.04	0.11±0.04	0.746
Impaired systolic function	EAT-Vol (mL)	75.3±23.4	75.1±23.0	0.981
	EAT-At-mean (HU)	-74.7±4.5	-76.3±4.3	0.309
	EAT-VI	0.10±0.04	0.11±0.03	0.849
Pericardial effusion	EAT-Vol (mL)	72.2±28.3	76.4±20.6	0.613
	EAT-At-mean (HU)	-71.9±4.0	-77.4±3.5	<0.001*
	EAT-VI	0.10±0.04	0.11±0.03	0.584
Critical illness	EAT-Vol (mL)	76.6±21.5	73.3±24.9	0.660
	EAT-At-mean (HU)	-75.4±4.6	-76.2±4.2	0.580
	EAT-VI	0.11±0.04	0.10±0.03	0.369

Data are shown as mean ± SD. *, significance of P value (P<0.05). ST/T changes include ST-segment elevation or depression, T-wave inversions. Impaired systolic function includes those impaired systolic left/right ventricle function, with or without increase in wall thickness, with or without dilated left/right ventricle on echocardiography or CMR. EAT, epicardial adipose tissue; EAT-Vol, epicardial adipose tissue volume; HU, Hounsfield units; EAT-VI, epicardial adipose tissue volume index; EAT-At, epicardial adipose tissue attenuation; SD, standard deviation; ST/T, ST-segment and T-wave; CMR, cardiac magnetic resonance.

Comparison of EAT measurements of AM-PE/nonPE patients with control patients

Considering the significant correlation between the presence of PE and the change in EAT-At in AM patients, further comparisons were carried out between the AM subgroups with and without PE and the control group. There was no difference of EAT-Vol among the 3 age groups, even controlling for the difference of heart volume between subjects. Whereas there was significant difference of EAT-At-mean among the three groups (ANOVA P=0.001), and so as to the quantitative histogram parameters, including EAT-At-SD, EAT-At-IQR, EAT-At5%, EAT-At10%, EAT-At25%, EAT-At75%, EAT-At90%, and EAT-At95% (data are shown in *Table 3*). In the presence of PE, mean EAT-At was significantly higher (-71.9±4.0 HU) when compared to the control group (-77.9±5.0 HU, Bonferroni corrected

P=0.001) and AM-nonPE group (-77.4±3.5, Bonferroni corrected P<0.001).

Discussion

In the present study, we found remodeling of the EAT in patients with AM comparing with controls, manifested as changes in volume or CT attenuation of EAT. We report for the first time that AM patients exhibited larger volume and higher mean attenuation of EAT than controls. Notably, changes in attenuation were significantly associated with the presentation of PE in AM patients. When AM was complicated with PE, we observed a significant increase in EAT-At compared to the control. There was a certain degree of reduction in volume which did not significantly differ from both controls and AM patients without PE.

Table 3 Comparison of EAT measurements of AM-PE/nonPE patients with control

Features	AM-PE (N=11)	AM-nonPE (N=27)	Control (N=52)	One-way ANOVA (P value)	Cp1 ^{&} (P value)	Cp2 ^{&} (P value)	Cp3 ^{&} (P value)
Age (years)	36.2±9.8	29.6±9.4	31.8±6.8	0.079	0.075	0.312	0.760
BMI (kg/m ²)	24.0±2.2	25.1±3.5	24.3±3.6	0.540	>0.99	>0.99	0.991
Heart-V (mL)	748.4±192.5	723.6±118.7	696.5±122.9	0.545	>0.99	0.919	>0.99
EAT-VI	0.10±0.04	0.11±0.03	0.09±0.03	0.127	>0.99	>0.99	0.136
EAT-Vol (mL)	72.2±28.3	76.4±20.6	64.7±26.0	0.129	>0.99	>0.99	0.147
EAT-At-mean (HU)	-71.9±4.0	-77.4±3.5	-77.9±5.0	0.001*	0.003*	<0.001*	>0.99
EAT-At-SD (HU)	31.2±1.7	32.9±2.0	33.1±2.4	0.042*	0.100	0.038*	>0.99
EAT-At-IQR (HU)	43.9±3.5	47.8±3.6	47.6±4.6	0.025*	0.036*	0.029*	>0.99
EAT-At 5% (HU)	-131±6.4	-138.8±7.3	-139.7±8.7	0.006*	0.025*	0.005*	>0.99
EAT-At 10% (HU)	-114.7±6.3	-123.1±6.6	-123.4±8.7	0.004*	0.011*	0.004*	>0.99
EAT-At 25% (HU)	-90.8±6.0	-98.5±5.3	-98.8±7.5	0.002*	0.006*	0.002*	>0.99
EAT-At 50% (HU)	-66.3±4.9	-72.7±3.9	-73.2±6.2	0.001*	0.004*	0.001*	>0.99
EAT-At 75% (HU)	-46.9±3.0	-50.7±2.3	-51.2±3.8	0.001*	0.006*	0.001*	>0.99
EAT-At 90% (HU)	-36.2±1.2	-37.9±1.1	-38.2±1.7	0.001*	0.006*	<0.001*	>0.99
EAT-At 95% (HU)	-32.8±0.8	-33.8±0.7	-33.8±0.8	0.001*	0.002*	0.001*	>0.99

Data are shown as mean ± SD. *, significance of P value; [&], Bonferroni correction is applied for post hoc multiple comparisons. Cp1 represent the result of comparison of AM-PE and AM-nonPE; Cp2 represent that of AM-PE and control; Cp3 represent that of control and AM-nonPE. EAT, epicardial adipose tissue; AM-PE, acute myocarditis with pericardial effusion; AM-nonPE, acute myocarditis without pericardial effusion; ANOVA, analysis of variance; BMI, body mass index; EAT-VI, epicardial adipose tissue volume index; EAT-Vol, epicardial adipose tissue volume; EAT-At, epicardial adipose tissue attenuation; HU, Hounsfield units; EAT-At-SD, standard deviation of EAT-At; EAT-At-IQR, interquartile range of EAT-At; SD, standard deviation.

The association of obesity and infection is found not only in nosocomial infections such as sternal wound infections or mediastinitis after cardiac surgery (15) but also in the H1N1 influenza and coronavirus disease 2019 (COVID-19) pandemics (16-18). In these processes, obesity-induced fat tissue remodeling and dysfunction play prominent roles (19). Adipocyte hyperplasia and hypertrophy cause fat tissue expansion, further leading to dysfunctional adipocytes and inflammation. Functionally, EAT secretes adipokines to maintain the equilibrium between protective and detrimental effects on the heart (7). When remodeling of EAT generates a chronic proinflammatory state, the imbalanced production of adipokines could directly or indirectly affect the myocardium. Most commonly, AM is initially caused by viral infection, resulting in distinct lymphocytic infiltration of the myocardium (20). Previous data suggest links of EAT and the secreted adipokines with not only chronic inflammation of myocardium leading to fibrosis and heart failure (21), but also acute inflammation

causing myocardial damage (6). The alterations in volume and attenuation observed in this study represent characteristics of remodeled EAT.

The interplay between EAT and the cardiovascular system is bidirectional, therefore, the remodeled EAT identified in this study may be linked to the risk of viral infection in the myocardium and myocardial injury in AM. Unfortunately, due to the lack of follow-up data, our results cannot determine the causal relationship between EAT remodeling and myocarditis. Increased volume of EAT has been found to be negatively correlated with the circulating concentration of adiponectin, which is a widely studied adipokine that can exert anti-inflammatory and immunomodulatory effects (5). Evidence has shown that reduced adiponectin is closely correlated with worse short-term outcomes in patients with fulminant myocarditis (22). Adiponectin can attenuate acute antiviral immune responses by suppressing innate immune responses and reducing the number and activation of NK cells (23). Weight loss and

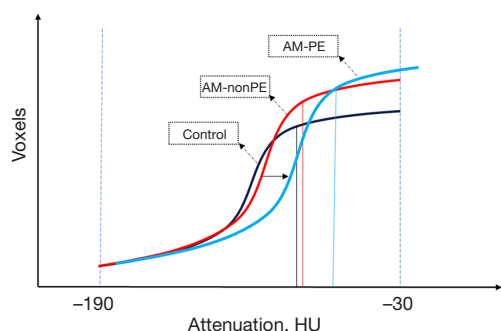


Figure 3 Schematic diagram of EAT attenuation histogram curve in acute myocarditis. EAT volume is linearly correlated with the total voxel count which is the area under the curve within the threshold of (-190, -30 HU). The vertical solid line in the figure represents the mean value of EAT attenuation. The morphology of histogram in acute myocarditis without pericardial effusion is similar to that of the control, with only an increase in volume. When pericardial effusion presented, EAT attenuation increases overall, reflected in larger averages, interquartile ranges and percentiles. The rightward shift resulted in a reduction in the number of voxels falling in the threshold range, ultimately leading to a computed decrease in EAT volume. AM-PE, acute myocarditis with pericardial effusion; AM-nonPE, acute myocarditis without pericardial effusion; HU, Hounsfield units; EAT, epicardial adipose tissue.

cardiac induction of adiponectin improve the survival and myocardial damage in mice with viral myocarditis (6). Last, increased volume of EAT is associated with the function and structure of the heart, such as abnormal right ventricle geometry, impaired left ventricular strain and diastolic function (10,11,24). Simultaneously, it is noteworthy that some myocarditis patients may exhibit persistent myocardial damage, potentially evolving into inflammatory cardiomyopathy with associated complications such as left ventricular dysfunction, heart failure, or arrhythmias, contributing to an adverse prognosis (25). Consequently, we posit that the remodeling of EAT likely plays a role in the recovery from myocarditis. However, the underlying relationship and mechanisms necessitate further investigation.

Even though the overall AM group showed a significant increment in mean attenuation of EAT, subgroup analysis revealed that this increase was primarily associated with the presence of PE. However, with the increase in attenuation, there was a slight reduction in volume of EAT, and it was

no longer significantly larger than control group. Indeed, the histogram analysis also revealed increases in all seven percentiles and the interquartile range. This indicates that the overall attenuation of EAT experienced an increase. Such change is visually represented on the histogram as a rightward shift of the entire curve, meaning it shifted towards higher values (Figure 3). Given the curve's left-low-right-high morphology, the rightward shift resulted in a reduction in the number of voxels falling within the threshold range of (-190 to -30 HU), ultimately leading to a computed decrease in volume. This explains the inconsistency observed in EAT volume comparisons between the groups with and without PE and the control group. And also, we need to point out that when employing the method of setting attenuation thresholds for quantitative analysis of EAT, the measured EAT volume and mean attenuation are interrelated. Therefore, in studies exploring relationships between EAT and diseases, especially when observing the dynamic changes of EAT, it is essential to consider both EAT volume and mean attenuation values comprehensively. This approach ensures a more comprehensive understanding of the pathophysiological alterations within EAT.

Two mechanisms could potentially explain the increase in attenuation seen here. One mechanism involves local inflammatory activation, a phenomenon observed in postmortem cases of lymphocytic myocarditis, where coexisting inflammation is detected in the left atrial and fat tissue as well (26). The other is transformation of white fat to brown or beige fat tissue with higher activity, which represent a progression to maintain metabolic homeostasis (3,27). In addition, an earlier study on pericarditis reported that lower EAT volume is associated with worse long-term clinical outcome (28), which goes against the common sense that high EAT volume would be associated with an increased risk of future cardiovascular events (12). It is unfortunate that this study did not measure EAT attenuation. However, there is reason to believe that the lower volume may be accompanied by higher attenuation of EAT, which suggests more severe inflammation or dysfunction within the adipose tissue. Future research necessitates long-term follow-up data on the dynamic changes of EAT to explore the prognostic value of EAT imaging features in predicting outcomes for AM.

The present study has some limitations. First, the retrospective and observational cohort design of the study makes it challenging to derive causality. Second, the sample size is small, mainly because CCTA had to be performed on

the same scanner because the attenuation is easily affected by the equipment. However, this compromise ensured the reliability of the results. Third, the subgroups based on symptoms are small and overlap with a risk of getting significant P values on coincidence. In the future, with more attention to abnormal EAT in myocarditis, larger observational cohorts may provide more comprehensive evidence. Fourth, none of the AM patients were confirmed by EMB or identified in the etiology. The diagnosis was made by the summation of clinical and imaging findings. Fifth, AM was most frequent in young people and also to minimize confusion with CAD, so their matched controls barely had CCTA data. Even though we carefully selected the control subjects, they might have had some unknown diseases and could bias the true EAT features in young population. Finally, this study did not include patients of older age with a higher prevalence of cardiovascular risk factors and comorbidities. Future research involving such populations should pay closer attention to the heterogeneity of intra- and inter-individual adipose tissue.

In conclusion, the present study found increased EAT volume in AM patients, suggesting that a connection exists between the underlying inflammation of remodeled EAT and the occurrence of AM. And when PE presented, the entire EAT attenuation increased. In addition, we recommend simultaneously evaluating EAT volume and attenuation when quantifying EAT using CT attenuation thresholds.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at <https://qims.amegroups.com/article/view/10.21037/qims-23-1407/rc>

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <https://qims.amegroups.com/article/view/10.21037/qims-23-1407/coif>). S.X. is an employee of Shanghai United Imaging Healthcare Co., Ltd. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by ethics board of Zhongshan Hospital of Fudan University (No. B2020-088R) and informed consent was taken from all the patients.

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