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Epicardial adipose tissue volume in patients with coronary artery disease or non-ischaemic dilated cardiomyopathy: evaluation with cardiac magnetic resonance imaging

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AIM: To compare the amount of epicardial adipose tissue (EAT) in patients with coronary artery disease (CAD) or non-ischaemic dilated cardiomyopathy (NIDCM) with that in patients with negative cardiac magnetic resonance imaging (CMR).

MATERIALS AND METHODS: One hundred and fifty patients (median age 57 years, interquartile range [IQR] 46–66 years) who underwent CMR were evaluated retrospectively: 50 with CAD, 50 with NIDCM, and 50 with negative CMR. For each patient, the EAT mass index (EATMI) to body surface area, end-diastolic volume index (EDVI), end-systolic volume index (ESVI), stroke volume (SV), ejection fraction (EF) for both ventricles, and left ventricle (LV) mass index were estimated. Intra and inter-reader reproducibility was tested in a random subset of 30 patients, 10 for each group. Mann–Whitney *U* test, Kruskal–Wallis test, Spearman's correlation, and Bland–Altman statistics were used.

RESULTS: The EATMI in CAD patients (median 15.7 g/m^2, IQR 8.3–25.7) or in NIDCM patients (15.9 g/m^2, 11.5–18.1) was significantly higher than that in negative CMR patients (9.1 g/m^2, 6–12; $p<0.001$ both). No significant difference was found between CAD and NIDCM patients ($p=1.000$). A correlation between EATMI and LV mass index was found in NIDCM patients

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(r=0.455, p=0.002). Intra- and inter-reader reproducibility were up to 80% and 72%, respectively.

CONCLUSION: Patients with NIDCM or CAD exhibited an increased EATMI in comparison to negative CMR patients. CMR can be used to estimate EAT with good reproducibility.

Introduction

Epicardial adipose tissue (EAT) is a fat deposit placed between the myocardium and the visceral layer of the pericardium while pericardial adipose tissue is a fat deposit on the external surface of the parietal pericardium, therefore, outside the EAT.[1,2] EAT is more represented in the atrio-ventricular and interventricular grooves and along coronary arteries. A smaller EAT volume is over the apex of the left ventricle, over the free wall of the right ventricle and around the atria.[3] Notably, the EAT is in direct contact with the myocardium, without any separating fascia and its blood supply is provided by the coronary arteries.[1]

Of note, EAT differs from pericardial adipose tissue, not only in its anatomy and embryological origin, but also in its physiology. In fact, while pericardial adipose tissue physiology is partially unknown,[4] EAT physiology has been widely studied. Three main functions have been defined: metabolic, thermogenic, and mechanical. Regarding metabolism, EAT has a greater uptake and release of free fatty acids and a lower glucose utilisation than all other fat deposits. This function is important for myocardial metabolism, which share coronary blood supply with EAT and is mainly based on free fatty acids oxidation.[5] The thermogenic role of EAT has been recently investigated: EAT should be considered similar to brown fat, defending the myocardium and coronary vessels against hypothermia. Interestingly, the number of brown adipocytes in adult EAT decreases with age[6] and, when EAT is activated by a cold stimulation, it shows a higher density value on computed tomography (CT).[7] Finally, EAT surrounds the coronary vessels, protecting them from the mechanical torsion induced by the arterial pulse.[8]

Under physiological conditions, EAT plays a cardioprotective role through the secretion of anti-atherogenic cytokines, while in pathological conditions the equilibrium is disrupted and this protective secretion is downregulated.[9] Meanwhile, EAT can upregulate the vasocrine or paracrine secretion of inflammatory and pro-atherogenic cytokines.[5]

Rabkin *et al.*[10] reviewed the literature regarding EAT and obesity. They found 26 studies showing positive correlation between EAT and body mass index (BMI) and 20 studies showing positive correlation between EAT and waist circumference. Moreover, these authors reported a positive correlation between EAT and metabolic syndrome as well as between EAT and four non-obesity components of metabolic syndrome such as high-density lipoprotein cholesterol, fasting blood glucose, systolic blood pressure, and triglycerides.[10]

A positive correlation between EAT volume and coronary artery disease (CAD),[11,12] atrial arrhythmias,[13] or adverse cardiovascular outcomes[14] has been reported; EAT is considered a predictor of clinical outcomes providing incremental prognostic value over traditional cardiovascular risk factors and coronary artery calcium scoring.[15]

The amount of EAT *in vivo* has been estimated in humans using different imaging methods: echocardiography, cardiac CT (CCT), and cardiac magnetic resonance imaging (CMR). Echocardiography, a radiation-free, ready available, and low-cost technique, can only measure EAT thickness and is difficult to perform in obese patients because of poor acoustic window.[16] Conversely, CCT involves ionising radiation exposure but has high spatial resolution and can measure not only EAT thickness but also the entire EAT volume.[15] Finally, CMR provides radiation-free images with a good spatial resolution, enabling measurement of the thickness and volume of the EAT.[17] The volume can be measured performing a slice-by-slice manual segmentation of the EAT area, multiplying each area by the section thickness to yield the EAT volume[17]; however, CMR is not widely accessible and it is a relatively high-cost technique.

Non-ischaemic dilated cardiomyopathy (NIDCM) is the most common non-ischaemic cardiomyopathy, defined as a left ventricular chamber dilation with systolic dysfunction with or without right ventricular dysfunction.[18] NIDCM has several causes, including infections, obesity, immunology system alterations, toxic injuries, or genetic factors.[19,20]

Considering the above-mentioned complex physiopathological role of the EAT, which also include a dual action in protecting from atherogenesis or triggering atherogenesis and inflammation, it was hypothesised that there was a correlation between EAT burden and severity of CAD and NIDCM. The aim of the present study was to compare the amount of EAT in patients with CAD or with NIDCM with that in patients with negative CMR.

Materials and methods

Study population

The local Ethics Committee approved this retrospective study (Ethics Committee of San Raffaele clinical research hospital; protocol code CardioFat; approved on July 13th, 2017). This study was supported by local research funds of Policlinico San Donato, a Clinical Research Hospital partially funded by the Italian Ministry of Health. Due to the retrospective nature of this study, no specific informed consent was necessary. Three series of 50 patients (CAD, NIDCM, and

negative) for a total of 150 patients who underwent a CMR between July 2013 and April 2015 were reviewed. No repeat examinations were included.

Image acquisition and analysis

All CMR examinations were performed using a 1.5 T Magnetom Sonata with 40-mT/m gradient power (up to September 2014) or a 1.5 T Magnetom Aera with 45-mT/m gradient power (after September 2014), using a four- or 12-channel surface phased-array coil placed over the thorax, respectively. Patients were studied in supine position.

CMR included a complete set of short-axis cine images from base to apex, using an electrocardiographically triggered steady-state free precession pulse sequence acquired with the following technical parameters: 4 ms time of repetition (TR), 1.5 ms time to echo, 80° flip angle, 8 mm section thickness, 45 ms time resolution, 14±4 seconds acquisition time (mean±standard deviation). Cine-images at end diastolic phase were used for segmentation.

For each patient, two independent readers (R1 and R2), with atleast 8 years of experience in CMR, performed measurements twice, with at least a 10-day interval between the two sessions, for a total of four sessions. They manually segmented EAT recognised as hyperintense tissue below pericardial sheet and above myocardium, including vessels, in each section. Partial volumes were obtained as a product of segmented area by section thickness; the total ventricular volume was obtained as a sum of all the partial volumes. The same method and software were also used to obtain RV and LV volumes and LV mass by contouring endocardial of RV and endocardial and epicardial of LV.

Both readers used the Argus software (version VA50A, Leonardo, Siemens Medical Solution, Erlangen, Germany) on a remote workstation.

Patients' disease classification

Patients were classified as being affected with CAD or NIDCM according to the following criteria: CAD was defined as a history of coronary occlusion (positive coronary angiography) confirmed by a CMR with positive typical delayed enhancement indicating ischaemic scar, and NIDCM was diagnosed by CMR criteria in association with negative coronary angiography to exclude post-ischaemic dilated cardiomyopathy.[21,22] Patients were considered as having a negative CMR when functional and morphological data were normal for both ventricles, without any delayed enhancement.

Data analysis

The EAT volume was converted into grams (EAT mass) multiplying it by 0.9196 g/cm^3.[21] The EAT mass was divided by the body surface area to obtain the EAT mass index (g/m^2). Data were presented as mean and SD or median and interquartile range (IQR), according to their normal/near-normal or non-normal distribution, respectively.

The different groups of patients (with CAD, NIDCM, or negative CMR) were compared using the Kruskal–Wallis test to evaluate the overall difference among the three groups and, subsequently, the Mann–Whitey test used to compare between pairs of subgroups. When indicated (repeated comparisons between the same two groups), the Bonferroni adjustment was used.

Spearman correlation test was used to correlate EAT volume with the left ventricular mass index (LVMI), and with end-diastolic volume index (EDVI), end-systolic volume index (ESVI), stroke volume (SV) and ejection fraction (EF) of both ventricles.

After bivariate analysis, multivariate linear regression analysis was performed to evaluate if both age and the groups are independent factors influencing the epicardial adipose tissue.

Using the Bland–Altman method, the intra- and inter-reader reproducibility values were estimated in a subset of 30 randomly selected patients (10 with CAD, 10 with NIDCM, 10 with negative CMR); for the inter-reader reproducibility, the first measurement of both readers was used. The coefficient of repeatability (CoR) was calculated as 1.96 × standard deviation of the differences of the two compared datasets. Reproducibility was reported as complement to 100% of the ratio between the CoR and the mean. Bland–Altman graphs were plotted, showing bias (mean of the differences of the two compared datasets), and 95% limits of agreement (bias±CoR).

Statistical analysis was performed using SPSS for Windows (v. 21.0, SPSS, Chicago, IL, USA) and Excel (Microsoft Excel 2010, Redmond, WA, USA). Two tailed p-value of <0.05 was considered statistically significant.

Results

In the present study population there were 107 males and 43 females with a median age of 57 years with an IQR of 46–66 years. All population details are reported in Table 1. Regarding the median value of BMI and body surface area, no significant differences ($p=0.265$ and $p=0.804$ respectively) were found among the three groups. A significant difference in terms of age was found in the three groups ($p<0.001$).

The median value of EAT mass index was 15.7 (IQR 8.3–25.7) g/m^2 in CAD patients, 15.9 (IQR 11.5–18.1) g/m^2 in NIDCM patients, and 9.1 (IQR 6–12) g/m^2 in patients with negative CMR. Comparing these three groups, a significant difference was found between patients with CAD or NIDCM versus negative CMR ($p<0.001$ for both comparisons). No significant difference for EAT mass index was found comparing CAD and NIDCM patients ($p=1.000$). All CMR parameters and comparisons are shown in Table 2.

Concerning the results of Spearman's correlation test, a correlation between EAT mass index and LVMI in NIDCM patients ($r=0.455$, $p=0.002$) was also found, while no significant correlations were found for the other groups. Moreover, no significant correlations were found between EAT and functional values of RV and LV. Multivariate linear regression analysis showed that the EAT is statistically different among the three groups of patients independently from age ($p=0.003$).

Table 1
Demographic characteristics of the study population.

	CAD patients	NIDCM patients	Patients with negative CMR	Overall *p*-value	Negative CMR vs CAD	Negative CMR vs NIDCM	CAD vs NIDCM
No. of patients	50	50	50	-			
Male/female	42/8	33/17	32/18				
Median age (years)	64 (60–71)	56 (49–64)	45 (37–54)	<0.001[a]	<0.001[a]	<0.004[a]	<0.003[a]
Body mass index (kg/m^2)	26.1 (24–28)	25.4 (23.3–27.4)	24.3 (22.2–27)	0.265	-	-	-
BSA (m^2)	1.9 (1.7–2)	1.9 (1.7–2)	1.9 (1.7–2.1)	0.804	-	-	-

Data are expressed as median and interquartile ranges.
CAD, coronary artery disease; NIDCM, non-ischaemic dilated cardiomyopathy; CMR, cardiac magnetic resonance; BSA, body surface area.
[a] Significant *p*-values.

Table 2
Cardiac magnetic resonance parameters.

	CAD patients	NIDCM patients	Patients with negative CMR	Overall *p*-value	Negative CMR vs CAD	Negative CMR vs NIDCM	CAD vs NIDCM
EAT ml	30 (16–54)	30 (25–38)	18 (12–26)	<0.001[a]	<0.001[a]	<0.001[a]	1.000
EAT mass index (g/m^2)	15.7 (8.3–25.7)	15.9 (11.5–18.1)	9.1 (6–12)	<0.001[a]	<0.001[a]	<0.001[a]	1.000
RVEDVI (ml/m^2)	57 (48–69)	65 (58–82)	73 (61–81)	0.001[a]	0.001[a]	0.615	0.061
LVEDVI (ml/m^2)	93 (78–111)	104 (87–121)	66 (60–76)	<0.001[a]	<0.001[a]	<0.001[a]	0.219
RVESVI (ml/m^2)	23 (17–33)	29 (23–41)	28 (24–33)	0.006[a]	0.076	1.000	0.006[a]
LVESVI (ml/m^2)	54 (37–74)	67 (49–84)	24 (18–29)	<0.001[a]	<0.001[a]	<0.001[a]	0.154
RVEF	60 (55–66)	52 (44–60)	59 (56–63)	<0.001[a]	<0.001[a]	<0.001[a]	1.000
LVEF	40 (31–50)	36 (30–43)	66 (58–73)	<0.001[a]	<0.001	<0.001[a]	0.317
LV mass index	89 (80–109)	96 (82–117)	67 (55–74)	<0.001[a]	<0.001[a]	<0.001[a]	1.000

Data are expressed as median and interquartile ranges.
CAD, coronary artery disease; NIDCM, non-ischaemic dilated cardiomyopathy; CMR, cardiac magnetic resonance; EAT, epicardial adipose tissue; RVEDVI, right ventricle end diastolic volume index; LVEDVI, left ventricle end diastolic volume index; RVESVI, right ventricle end systolic volume index; LVESVI, left ventricle end systolic volume index; RVEF, right ventricle ejection fraction; RVEF, left ventricle ejection fraction; LV, left ventricle.
[a] Significant *p*-values.

The image analysis was feasible in all patients and no artefacts prevented correct segmentation of EAT. The time required for measurement was approximately 5 minutes for both readers.

The Bland–Altman plots showed a mean of 34.7 ml with a bias of 0.7 ml and a CoR of 5.8 ml for the intra-reader reproducibility (Fig 1a); while a mean of 33.8 ml with a bias of −0.9 ml and a CoR of 8.2 ml was found for the inter-reader reproducibility (Fig 2a).

The Bland–Altman plots in CAD patients showed a mean of 39.6 ml with a bias of 2.3 ml and a CoR of 6.4 ml for intra-reader reproducibility (Fig 1b); while the mean was 38.4 ml with a bias of −0.10 ml and a CoR of 8 ml for the inter-reader reproducibility (Fig 2b).

The Bland–Altman plots in NIDCM patients showed a mean of 39.3 ml with a bias of 0.04 ml and a CoR of 5.3 ml for the intra-reader reproducibility (Fig 1c); while the mean was 37.5 ml with a bias of −3.5 ml and a CoR of 7.4 ml for inter-reader reproducibility (Fig 2c).

The Bland–Altman plots in negative CMR showed a mean of 25.1 ml with a bias of -0.2 ml and a CoR of 4.9 ml for the intra-reader reproducibility (Fig 1d); while the mean was 25.6 ml with a bias of 0.8 ml and a CoR of 7.1 ml for the inter-reader reproducibility (Fig 2d).

Example of EAT segmentation in the three groups is showed in Fig 3.

Discussion

The main findings of the present study were that (1) the EAT mass index in CAD patients (15.7 g/m^2) or in NIDCM patients (15.9 g/m^2) was significantly higher than in negative CMR patients (9.1 g/m^2), although no significant difference was found between CAD and NIDCM patients; (2) in NIDCM patients, the EAT mass index was positively correlated with left ventricle mass; (3) a routine CMR protocol enables estimation of the EAT volume with good intra- and inter-reader reproducibility.

The role of EAT has been well studied and its role as a biologically active organ rather than a fat deposit is now well established. In particular, EAT volume has been shown to be positively correlated with a broad spectrum of disorders such as CAD, metabolic syndrome, insulin resistance, and fatty liver disease.[16,23] Because of the correlation of EAT with BMI and clinical indicators of obesity,[10] the present values regarding body surface area were normalised using EAT mass index; however, no significant differences in BMI and body surface area values were found among the three groups. When comparing CAD patients with NIDCM patients, a significant difference was found in age but not in EAT, a combination of results indicating a negligible influence of age on EAT.

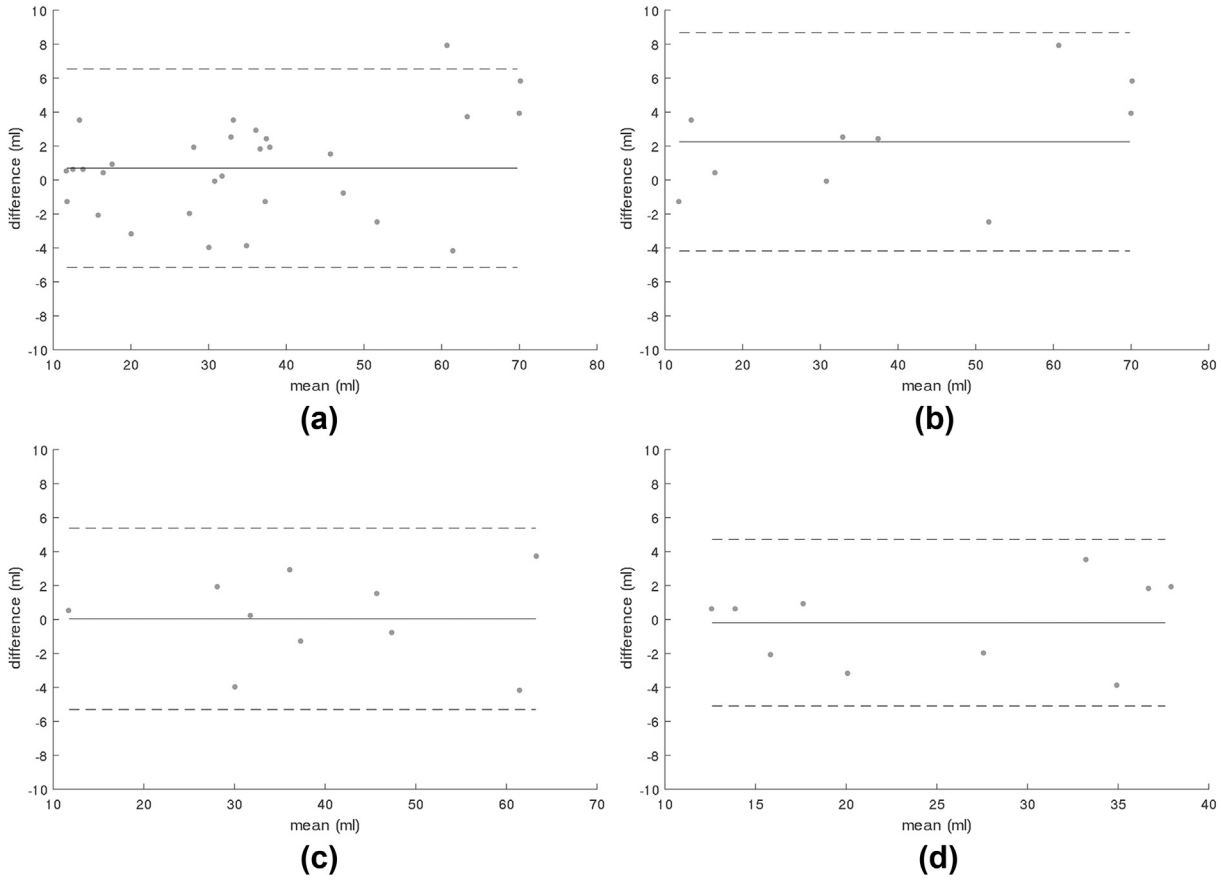

Figure 1 Bland–Altman plots for intra-reader reproducibility analysis of the first reader: (a) overall, the mean was 34.7 ml with a bias of 0.7 ml, and a coefficient of repeatability of 5.8 ml; (b) in CAD patients, the mean was 39.6 ml with a bias of 2.3 ml, and a coefficient of repeatability of 6.4 ml; (c) in NIDCM patients, the mean was 39.3 ml with a bias of 0.04 ml, and a coefficient of repeatability of 5.3 ml, and (d) patients with negative CMR, the mean was 25.1 ml with a bias of −0.2 ml, and a coefficient of repeatability of 4.9 ml.

The relation between EAT and CAD has been already reported,[24] investigating the relation between increased EAT, the presence of CAD, and plaque vulnerability, higher rate of cardiac death and myocardial infarction.[25,26] The EAT thickness was also shown to predict adverse cardiac events in patients admitted with angina or myocardial infarction.[14] Thus, the present results provide additional evidence to the relation between EAT and CAD.

Conversely, the correlation of the EAT mass index and NIDCM was not so clear. Doesch *et al.*[27] demonstrated a significantly lower EAT mass index in NIDCM patients (24 ± 7.5 g/m^2) compared with healthy subjects (31.7 ± 5.6 g/m^2); however, their control group had a higher EAT mass index values than the present study (see Table 1). In addition, they included NIDCM patients with a left ventricle ejection fraction (28.2 ± 11.2%, mean±standard deviation) that was lower than the present NIDCM patients (36%, 30–43%, median, IRQ). Another study published by the same group[23] demonstrated a reduced EAT mass index in patients with heart failure irrespective of the cause of heart insufficiency. Thus, the role of ejection fraction should be considered when comparing EAT mass index in different studies, as demonstrated by Tabakci *et al.*[28] using echocardiography.

A significant increased EAT mass index was found in patients with NIDCM compared to patients with negative CMR. In NIDCM patients with relative preserved ejection fraction, EAT values can be higher than in normal subjects, while in NIDCM with heart failure EAT values decrease.[23] In addition, in NIDCM patients a positive correlation between LVMI and EAT mass index was found, which in line with the fact that an hypertrophic heart with increased left ventricle mass is positively associated with the EAT.[26] In patients with NIDCM, a dilated heart causes overall enlargement of the heart, which implies, paradoxically, an increased left ventricle mass.

The Bland–Altman limits were typically ±6 ml and, given the absence of reference values, this is of little clinical relevance. The sub-group analysis for reproducibility showed good intra-reader and inter-reader reproducibility, as expected.[23] This result confirms the role of CMR as a reliable radiation-free tool for EAT volume estimation in clinical practice. The variation is clinically acceptable because the difference in EAT mass index between patients and healthy subjects is so great that variation does not affect the ability to discriminate between the two groups.

There are limitations to the present study. First, because of the retrospective design, there is no detailed clinical

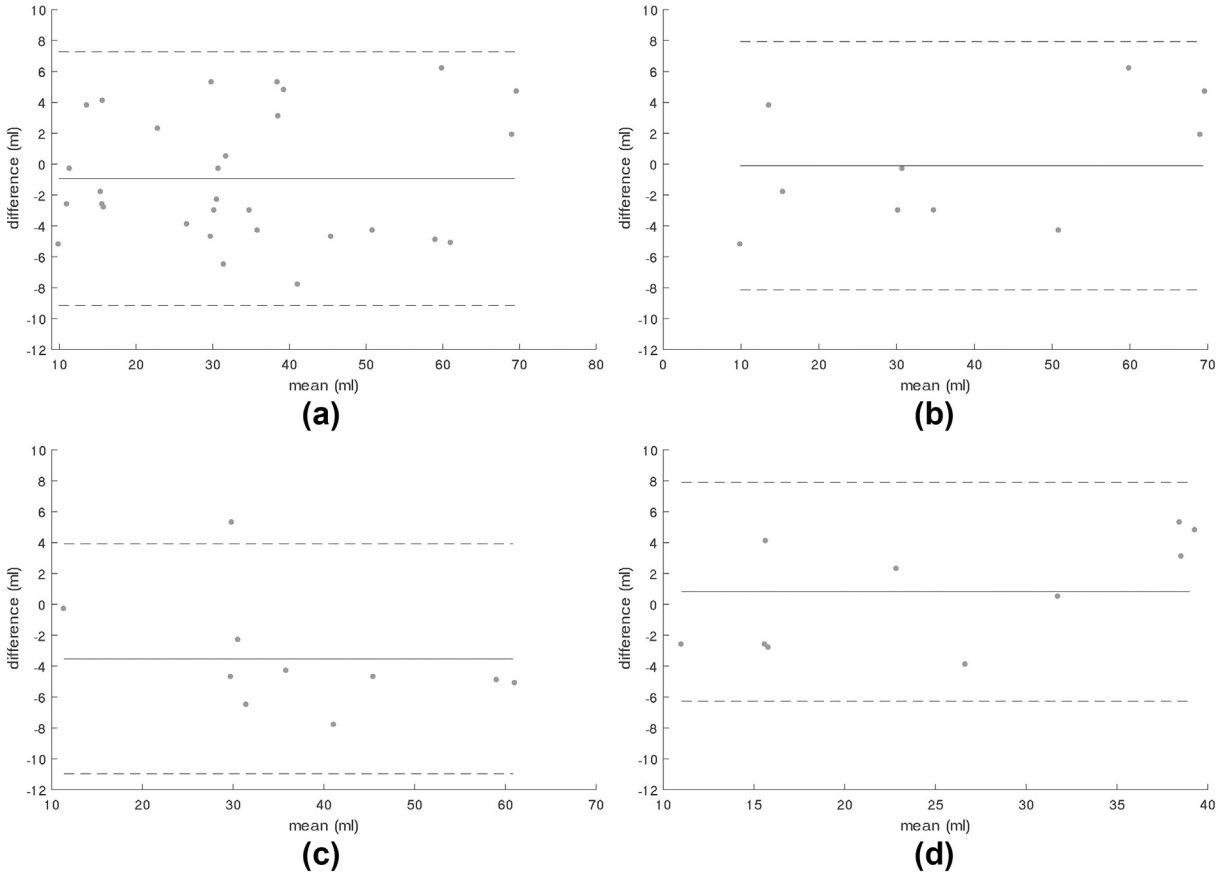

Figure 2 Bland–Altman plots for inter-reader reproducibility analysis: (a) overall, the mean was 33.8 ml with a bias of −0.9 ml, and a coefficient of repeatability of 8.2 ml; (b) in CAD patients, the mean was 38.4 ml with a bias of −0.10 ml, and a coefficient of repeatability of 8 ml; (c) in NIDCM patients, the mean was 37.5 ml with a bias of −3.5 ml, and a coefficient of repeatability of 7.4 ml and d patients with negative CMR, the mean was 25.6 ml with a bias of 0.8 ml, and a coefficient of repeatability of 7.1 ml.

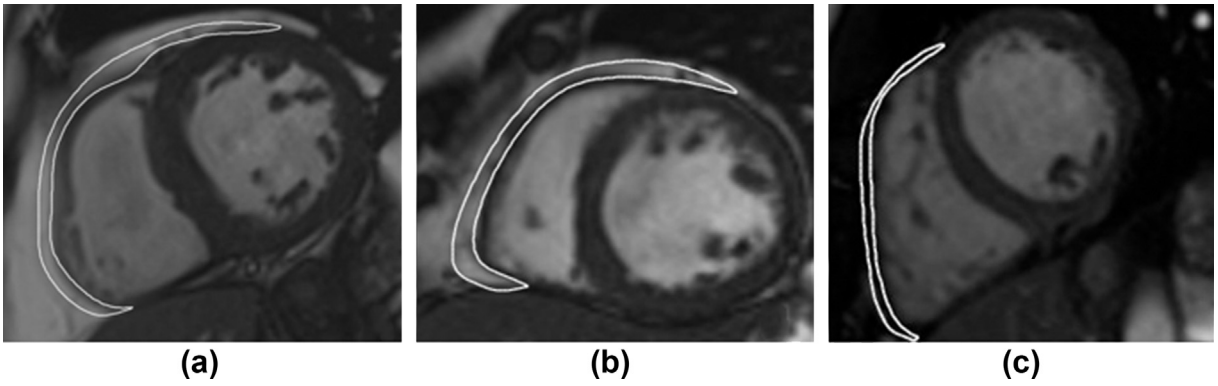

Figure 3 Examples of epicardial adipose tissue segmentation on mid-ventricle short-axis CMR images in patients with (a) CAD, (b) NIDCM, and (c) negative examination. The total EAT mass indexed was 45 g/m^2 in patient A, 28.3 g/m^2 in patient B, and 5.9 g/m^2 in patient C. The figure demonstrates the possible difficulty in measuring small quantities of epicardial fat, such as that along the free left ventricular wall.

information regarding aetiology, cardiovascular risk factors, and stages of NIDCM in the present patients. Thus, no subgroup analysis could be performed for a deeper insight on the role of EAT in NIDCM. Second, CAD patients and NIDCM patients were compared with a control group composed with patients with negative CMR irrespective of the clinical suspicion for which they underwent CMR; however, due to the high sensitivity of CMR, it can be assumed that those patients with a completely negative CMR were mostly free from clinically relevant structural heart disease. Conversely, the possible underestimation of heart diseases in negative CMR patients, if any, would have

played against a higher EAT mass index in CAD or NIDCM patients versus negative CMR patients, reinforcing the value of the present results. Moreover, the present study was small, using CMR, with limited spatial resolution, to estimate EAT mass index.

In conclusion, a significant increase in the EAT mass index was observed in patients with CAD or NIDCM compared to negative CMR patients. Further studies are needed to confirm the variation of these values in NIDCM patients stratified by disease stages. An interesting perspective will be the evaluation of the EAT mass index in longitudinal cohort studies of patients with different heart disease in order to elucidate the correlation with disease course as well as potential targets for prevention and treatment.

Conflicts of interest

The authors declare no conflict of interest.

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