Original Article
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Obesity

Epicardial Adipose Tissue Assessed by Cardiac Magnetic Resonance Imaging in Patients with Heart Failure Due to Dilated Cardiomyopathy

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Objective: We sought to investigate the association of the EAT with CMR parameters of ventricular remodelling and left ventricular (LV) dysfunction in patients with non-ischemic dilated cardiomyopathy (DCM).

Design and Methods: One hundred and fifty subjects (112 consecutive patients with DCM and 48 healthy controls) underwent CMR examination. Function, volumes, dimensions, the LV remodelling index (LVRI), the presence of late gadolinium enhancement (LGE) and the amount of EAT were assessed.

Results: Compared to healthy controls, patients with DCM revealed a significantly reduced indexed EAT mass (31.7 $\pm$ 5.6 g/m^2 vs 24.0 $\pm$ 7.5 g/m^2, p<0.0001). There was no difference in the EAT mass between DCM patients with moderate and severe LV dysfunction (23.5 $\pm$ 9.8 g/m^2 vs 24.2 $\pm$ 6.6 g/m^2, $P = 0.7$). Linear regression analysis in DCM patients showed that with increasing LV end-diastolic mass index (LV-EDMI) ($r = 0.417$, $P < 0.0001$), increasing LV end-diastolic volume index ($r = 0.251$, $P = 0.01$) and increasing LV end-diastolic diameter ($r = 0.220$, $P = 0.02$), there was also a significantly increased amount of EAT mass. However, there was no correlation between the EAT and the LV ejection fraction ($r = 0.0085$, $P = 0.37$), right ventricular ejection fraction ($r = 0.049$, $P = 0.6$), LVRI ($r = 0.116$, $P = 0.2$) and the extent of LGE % ($r = 0.189$, $P = 0.1$). Among the healthy controls, the amount of EAT only correlated with increasing age ($r = 0.461$, $P = 0.001$), BMI ($r = 0.426$, $P = 0.003$) and LV-EDMI ($r = 0.346$, $P = 0.02$).

Conclusion: In patients with DCM the amount of EAT is decreased compared to healthy controls irrespective of LV function impairment. However, an increase in LV mass and volumes is associated with a significantly increase in EAT in patients with DCM.

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Introduction

Non-ischemic dilated cardiomyopathy (DCM) is characterized by left ventricular (LV) dilatation and a progressive impairment of cardiac contractility (1). Activation of macrophages and fibroblasts (2) as well as inflammatory processes seem to play an important role in the propagation of a diffuse interstitial and perivascular fibrosis (3) that is supposed to lead to cardiac remodeling in these patients.

Epicardial adipose tissue (EAT) is a metabolically active tissue, secreting several adipokines with pro- and anti-inflammatory properties (4–6). So far, the role of EAT has been studied mainly in the development of coronary artery disease (CAD) (7,8). Additionally, recent studies showed decreased amounts of EAT in patients with congestive heart failure irrespective of the underlying cause (9–11). Furthermore, in consecutive patients undergoing cardiac computed tomography to rule out significant coronary artery stenosis, analysis of epicardial fat volume revealed a stepwise decrease in patients with moderate to severe LV dysfunction compared to controls (11). However, to date, there are scarce data about the role of EAT in the development of heart failure in patients with DCM. Therefore, the aim of our study was to investigate the association of the EAT amount with the severity of the LV dysfunction and parameters of ventricular remodeling using CMR.

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Methods

Study population

One hundred twelve consecutive patients with DCM (87 males and 25 females; mean age 59.4±13.9 years) who were referred to our hospital between January 2007 and December 2010 were recruited. The cardiac magnetic resonance imaging (CMR) study was performed in these patients as part of the clinical evaluation for patients with known or suspected cardiomyopathy at our institution. In patients with chronic renal failure and an estimated glomerular filtration rate (GFR) <30 ml/min/1.73m^2, the CMR protocol was performed without the administration of a contrast agent. The diagnosis of DCM was made according to the World Health Organization/International Society and Federation of Cardiology criteria (12). Patients had to exhibit a depressed LV systolic function, that is, LV ejection fraction (LVF) < 50% on a non-CMR study in the absence of significant CAD defined as coronary artery stenoses ≥ 50% or a history of coronary revascularization or previous myocardial infarction. Patients with valvular heart disease, hypertensive heart disease, or congenital abnormalities were also not included. None of the patients showed signs or symptoms of ongoing myocarditis. Patients with a normal LVF on CMR > 55% were excluded.

Forty-eight age- and sex-matched healthy subjects served as controls and satisfied the following criteria: normal physical examination, normal blood pressure (systolic blood pressure <130 mm Hg and diastolic blood pressure <85 mm Hg), normal ECG findings, no history of chest pain or dyspnea, no diabetes, no hyperlipidemia, and normal 2D echocardiography and Doppler examination. None of the subjects was on medication. Any potential subjects with evidence of heart disease, hypertension, or other systemic disorders were excluded from the study.

All patients and volunteers underwent CMR examination with identical protocols. Informed consent for the CMR protocol was obtained from all subjects, and the study was approved by the local ethics commission.

Image acquisition

All studies were performed using a 1.5 Tesla whole-body imaging system (Magnetom Avanto, Siemens Healthcare Sector, Erlangen, Germany). A dedicated six-element, phased-array cardiac coil was used. Images were acquired during repeated end-expiratory breath-holds. Scout images (coronal, sagittal, and axial planes) were obtained for planning of the final double-oblique long-axis and short-axis views. To evaluate functional parameters, electrocardiogram-gated cine images were then acquired using a segmented steady-state free precession [fast imaging with steady-state precession (true-FISP)] sequence (time to echo/time of repetition 1.6/3.2 ms, temporal resolution 35 ms, in-plane spatial resolution 1.4×1.8 mm, slice thickness 8 mm, and interslice gap 2 mm). Seven to twelve short-axis views covering the whole left and right ventricle were obtained. For the assessment of the EAT, we used a dark blood prepared T1-weighted multislice turbo spin-echo pulse sequence with a water suppression prepulse to obtain a transversal four-chamber view and short-axis images in the same orientations used for the cine short-axis images. Imaging parameters were as follows: time of repetition = 800 ms, time to echo = 24 ms, slice thickness = 6 mm, interslice gap = 2 mm, and field of view = 30-34 cm.

Late gadolinium enhancement

Late gadolinium enhancement (LGE) images in the same orientation as the cine images were acquired 10 min after the intravenous administration of a gadolinium-based contrast agent (Magnevist, Bayer-Schering Pharma AG, Berlin, Germany), using an inversion recovery Turbo FLASH 2D sequence: field of view 300-340 mm, TR 9.56 ms, TE 4.38 ms, flip angle 25°; matrix, 166 × 256, and slice thickness 6 mm. Inversion time was individually adjusted to optimally null myocardial signal (200-360 ms). In all patients, imaging was repeated for each short-axis image in two separate phase-encoding directions to exclude artifacts.

Image analysis and determination of ventricular parameters

Image analysis and quantitative analysis were performed offline using the dedicated software (ARGUS, Siemens). Each study was examined for abnormalities in the morphology of the right and left ventricle. End-diastolic (EDV) and end-systolic volumes (ESV) and LV mass were analyzed with the serial short-axis true-FISP cine loops, using manual segmentation. Stroke volumes and LV and right ventricular (RV) ejection fractions were calculated. Additionally, LV and RV diameters were measured.

For the LV ejection fraction (LVF), the most basal section was the section that at end diastole and end systole still showed a wall thickness that was compatible with the LV myocardium and that extended over at least 50% of the myocardial circumference. At end systole, the most basal section could also show a part of the LV outflow tract or the mitral valve leaflets. The most basal section could differ by one section position between end diastole and end systole (13). For the right ventricle (RV), volumes below the pulmonary valve were included. From the inflow tract, RV volumes were excluded if the surrounding muscle was thin and not trabeculated, suggestive of right atrium (14).

Additionally, the LV remodeling index (LVRI) was calculated as the ratio of LV mass (LV-EDM) to LV volume (LV-EDV) (15).

Relative wall thickness (RWT) was calculated as follows: [2 × LV posterior wall thickness/LV end-diastolic diameter (LV-EDD)] (16). A value 0.45 was defined as abnormal. An LV-EDMI >71.5 g/m^2 for men and >66.6 g/m^2 for women were used to define the presence of LV hypertrophy (14). According to the values of LV-EDMI and RWT, the patients were categorized into four geometric patterns: normal (normal LV-EDMI and normal RWT), concentric remodeling (normal LV-EDMI and increased RWT), eccentric LV hypertrophy (LVH) (increased LV-EDMI and normal RWT), and concentric LVH (increased LV-EDMI and increased RWT) (17).

Volumetric assessment of the absolute mass of EAT

EAT is located between the outer wall of the myocardium and the visceral layer of pericardium. Therefore, we draw one line along the myocardial border and a second one at the visceral layer of the pericardium, subtending the area of EAT between these lines (18). For EAT mass determination, the area subtended by the manual tracings was determined on consecutive end-diastolic short-axis slice beginning with the most basal slice at the level of the mitral valve and moving apically through the stack until the most inferior margin of EAT was traced (18). Total EAT volume was obtained after the data summation of all slices (EAT volume = $\sum$ [EAT area × (slice thickness + interslice gap) using the modified Simpson's rule (19). To obtain EAT

mass, the EAT volume was multiplied by the specific weight of fat (0.92 g/cm^3). The observer was blinded to patient details.

Presence of LGE

The presence of LGE was assessed visually by two independent experienced readers blinded to all patient details. LGE was only considered to be present if it was also present in the same slice after swapping phase encoding, thus excluding artifacts. Patients were divided into those with enhancement (LGE+) and those without (LGE−). The pattern of LGE was characterized as mid-wall, subendocardial extending to epicardial surface, patchy foci, epicardial, or diffuse (20,21). For quantification of fibrosis, LGE was defined as areas with a signal intensity $>$ 2 standard deviations (SD) above mean signal intensity of remote myocardium in the same short-axis slice (22). Areas were measured by manual planimetry and expressed as percentage of the myocardial area using the VPT tool (Siemens Healthcare Systems Erlangen, Germany).

Statistical analysis

Body mass index (BMI) was calculated by the common formula: BMI (kg/m^2) = weight (kg)/height (m)^2. Body surface area (BSA) was assessed by a variation of the DuBois and DuBois formula: BSA (m^2) = [weight (kg)$^{0.425}$ $\times$ height (cm)$^{0.725}$] $\times$ 0.007184 (23). The Kolmogorow-Smirnow test was used to test for normality. The data are presented as mean $\pm$ SD for normally distributed quantitative variables and n (%) for qualitative variables. Data that are not normally distributed are given as medians and interquartile ranges. Continuous variables between two groups were analyzed by the unpaired, two-tailed student's t-test. The Mann-Whitney U test (Chi-square test) was applied for nonparametric data. A P-value $<$0.05 was considered statistically significant. Univariate linear regression analysis was performed to correlate the indexed EAT mass with CMR parameters in patients with DCM and in healthy controls. A multiple regression analysis adjusted for age and BMI was performed among patients with DCM to identify independent correlates of EAT.

Analysis was performed using the SPSS statistical software (version 14.0, SPSS, Chicago, Illinois).

Results

Patient characteristics

Patients' baseline demographic and clinical characteristics are summarized in Table 1. Our patient cohort consisted of 112 patients with DCM [thereof 87 men (78%)] with a mean $\pm$ SD age of 59.4 $\pm$ 13.9 years and 48 sex- and age-matched healthy controls. There were no significant differences, regarding body weight, BSA, and BMI between patients with DCM and healthy controls. The majority of DCM patients with moderate LV dysfunction had no or only mild symptoms NYHA (New York Heart Association) class I/II 15/28 (54%), whereas 71/84 (85%) with severe dysfunction were in NYHA class III/IV. In adherence with current treatment guidelines, DCM patients with LVF $\leq$ 35% received significantly more ACE/ARB, diuretics, and digoxin than those with LVF $>$35% due to standard heart failure treatment (Table 1).

CMR parameters

Table 2 summarizes the CMR characteristics of all DCM patients and healthy controls. In 35 patients, no LGE study was performed due to chronic renal failure GFR $<$ 30 ml/min/1.73 m^2 (n = 20), patient's refusal of contrast agent administration (n = 8), and discontinuation of CMR examination due to dyspnea before performance of the LGE study (n = 7). Among the 77 DCM patients with a LGE study, LGE was present in 24/77 (31%) with the following regional patterns: septal midwall 13/24 (54%), subendocardial extending to the epicardial surface 3/24 (12.5%), patchy foci 7/24 (29.3%), epicardial 1/24 (4.2%), and diffuse 0/24. Among patients with LGE, the median extent of fibrosis was 8.3% of LV mass (range 5.6-11.5 %). The presence of LGE and the extent of LGE % were not significantly different in patients with moderate [3/21 (14%), 4.8% (2.8-6.9 %)] and severe LV dysfunction [21/56 (38%), P = 0.09, 8.3% (6.9-12.5 %), P = 0.2)]. However, the EAT mass in DCM patients with LGE was slightly but not statistically significant higher compared to those without LGE (26.4 $\pm$ 8.8 g/m^2 vs. 23.3 $\pm$ 8.1 g/m^2, P = 0.1). Compared to healthy controls, the EAT mass was significantly reduced in all patients with DCM (31.7 $\pm$ 5.6 g/m^2 vs. 24.0 $\pm$ 7.5 g/m^2, $P <$ 0.0001) as well as in the subgroup analysis of DCM patients with moderate DCM (31.7 $\pm$ 5.6 g/m^2 vs. 23.5 $\pm$ 9.8 g/m^2, $P <$ 0.0001) and severe LVF impairment (31.7 $\pm$ 5.6 g/m^2 vs. 24.2 $\pm$ 6.6 g/m^2, $P <$ 0.0001). Although functional and volumetric parameters revealed an association with the degree of LV dysfunction, the EAT mass did not differ between DCM patients with moderate and severe LV dysfunction (23.5 $\pm$ 9.8 g/m^2 vs. 24.2 $\pm$ 6.6 g/m^2, P = 0.7).

Correlation between EAT mass and parameters of LV remodeling

In DCM patients, the EAT mass /LV mass ratio as well as the EAT mass /LV volume ratio were significantly reduced compared to healthy controls, and the reduction was most pronounced in patients with severe LV dysfunction (Table 2, Figure 1). According to the values of LV-EDMI and RWT, 13 of the 112 patients with DCM (11.6%) showed a non-hypertrophied geometric pattern. The other 99/112 (88.4%) showed eccentric LV hypertrophy (LVH) with increased LV-EDMI and normal RWT. 47/99, (47.5%) of DCM patients with an eccentric LVH had concomitant arterial hypertension. Looking at the EAT mass in the patients with eccentric LVH, we found that it was significantly elevated compared to the DCM patients without LVH (24.4 $\pm$ 7.1 g/m^2 vs. 18.5 $\pm$ 6.4 g/m^2, P = 0.01), however, significantly less than that in healthy controls (24.4 $\pm$ 7.1 g/m^2 vs. 31.7 $\pm$ 5.6 g/m^2, $P <$ 0.0001). Compared to the EAT mass in the 54/112 DCM patients with arterial hypertension and the 58/122 DCM patients without arterial hypertension, we did not find a difference (24.0 $\pm$ 6.8 vs. 24.0 $\pm$ 8.1, P = 0.97).

Association between the indexed EAT and CMR parameter

By univariate regression analysis (Table 3), increasing indexed EAT mass in all 112 patients with DCM correlated with increasing LV end-diastolic mass index (LV-EDMI) ($P <$ 0.0001), increasing LV end-diastolic volume index (LV-EDVI) (P = 0.01), increasing LV end-systolic volume index (LV-ESVI) (P = 0.01), increasing LV end-diastolic diameter (LV-EDD) (P = 0.02) as illustrated in Figure 2. Among these parameters, multiple regression analysis adjusted for age and BMI revealed that LV-EDMI (P = 0.001) was the only independent correlate with EAT. Besides, male DCM patients showed more indexed EAT mass than women (P = 0.04). However, no correlation was found between indexed EAT mass and LVF (P = 0.37), LVRI (P = 0.2), RV-EDD (P = 0.3), RVF (P = 0.6), RV-EDVI (P = 0.05), RV-ESVI (P = 0.1), or presence of LGE (P = 0.1).

TABLE 1 Demographic and baseline clinical characteristics: Healthy controls and patients with DCM

	Patients with DCM					
	LVF >35% ($n = 28$)	LVF ≤35% ($n = 84$)	P^*	All patients with DCM ($n = 112$)	Healthy controls $n = 48$	$P^¥$
Age (years)	57.2 ± 13.4	60.1 ± 14.0	0.3	59.4 ± 13.9	60.9 ± 9.8	0.5
Male sex, *n* (%)	22 (79)	65 (77)	0.99	87 (78)	37 (77)	0.99
Body weight (kg)	82.4 ± 15.2	82.5 ± 17.1	0.98	82.5 ± 16.6	81.9 ± 14.5	0.8
BSA (m^2)	2.0 ± 0.2	2.0 ± 0.2	0.6	2.0 ± 0.2	2.0 ± 0.2	0.9
BMI (kg/m^2)	26.6 ± 4.6	27.3 ± 4.8	0.5	27.2 ± 4.7	27.3 ± 6.0	0.9
Systolic BP (mm Hg)	111.5 ± 9.3	108.0 ± 14.3	0.2	108.9 ± 13.2	124.0 ± 6.0	<0.0001
Diastolic BP (mm Hg)	74.6 ± 5.8	71.9 ± 7.1	0.07	72.6 ± 6.9	80.9 ± 8.0	<0.0001
Heart rate (beats/min)	83.9 ± 9.7	78.1 ± 17.9	0.1	79.6 ± 16.3	70.2 ± 11.4	0.0004
Atrial fibrillation, *n* (%)	8 (29)	28 (33)	0.9	36 (32)	0	–
Hypertension, *n* (%)	13 (46)	41 (49)	0.9	54 (48)	0	–
Diabetes, *n* (%)	2 (7)	27 (32)	0.02	29 (32)	0	–
Smoking, *n* (%)	2 (7)	18 (21)	0.2	20 (18)	0	–
Family history of DCM , *n* (%)	3 (11)	5 (6)	0.7	8 (7)	0	–
Time since diagnosis (years)	2.4 ± 3.4	4.6 ± 3.3	0.004	4.0 ± 3.4	–	–
NYHA functional class, n (%)						
I	11 (39)	2 (2)	<0.0001	13 (12)	48 (100)	<0.0001
II	4 (14)	11 (13)	0.7	15 (13)	0	–
III	13 (46)	38 (45)	0.9	51 (46)	0	–
IV	0	33 (39)	-	33 (29)	0	–
Medications						
ACEI /ATII, *n* (%)	11 (39)	69 (82)	<0.0001	80 (71)	0	–
Beta blockers, *n* (%)	5 (18)	11 (13)	0.8	16 (14)	0	–
Spironolactone, *n* (%)	3 (11)	24 (29)	0.4	97 (87)	0	–
Diuretics, *n* (%)	8 (20)	69 (82)	<0.0001	77 (69)	0	–
Angicoagulation, *n* (%)	13 (46)	56 (67)	0.1	69 (62)	0	–
Digoxine, *n* (%)	2 (7)	28 (33)	0.01	30 (27)	0	–
Amiodarone, *n* (%)	2 (7)	2 (2)	0.6	4 (4)	0	–
Statins, *n* (%)	14 (50)	51 (61)	0.4	65 (58)	0	–

P^*-value comparing DCM patients with moderate and severe LV dysfunction, $P^¥$-value comparing all patients with DCM and healthy controls. The data are presented as mean ± standard deviation (SD) for normally distributed quantitative variables and *n* (%) for qualitative variables.

In the healthy controls, increasing EAT was significantly correlated with increasing age ($P = 0.001$), increasing BMI ($P = 0.003$), and increasing LV-EDMI ($P = 0.02$) as shown in Figure 3.

Discussion

The main findings of the study are as follows: (1) in patients with DCM, the amount of EAT is significantly reduced compared to healthy controls; (2) in patients with DCM, LV remodeling reflected by an increase in LV diameter, volumes, and mass significantly correlates with the EAT mass; and (3) the EAT amount in patients with DCM is irrespective of the LV function impairment.

EAT is a metabolically active tissue and a source of various bioactive molecules (4,6,24). Due to its close anatomic relationship to the adjacent myocardium, it is suggested to affect and modulate cardiac function and morphology (24–26). Both unfavorable and protective effects have been attributed to EAT (27,28). In patients with CAD, the amount of EAT has shown to be significantly correlated with the extent and the severity of CAD (7,29–31). However, little is known about the role of EAT in patients with DCM. In previous studies of our group (9,10), we compared patients with HF and severely reduced LVF (<35%) due to ICM or DCM and healthy controls. We could show that in patients with HF, EAT mass was significantly reduced, compared to healthy controls. This reduction was irrespective of the underlying etiology of HF. However, in this study, we only included patients with severely LVF impairment.

In the present study, we investigated the association between the amount of EAT and CMR parameters of ventricular remodeling solely in patients with DCM and different degrees of LV function impairment compared to age-matched controls. All patients with

TABLE 2 CMR characteristics: Healthy controls and patients with DCM

	Patients with DCM					
	LVF >35% ($n = 28$)	LVF ≤35% ($n = 84$)	P^*	All patients with DCM ($n = 112$)	Healthy controls $n = 48$	$P^¥$
LVF (%)	43.6 ± 6.9	23.0 ± 6.7	<0.0001	28.2 ± 11.2	58.7 ± 5.2	<0.0001
LV-EDMI (g/m^2)	84.2 ± 26.9	110.3 ± 8.2	<0.0001	104.1 ± 29.7	65.1 ± 11.4	<0.0001
LV-EDVI (ml/m^2)	102.8 ± 34.2	156.9 ± 44.9	<0.0001	143.9 ± 48.5	73.7 ± 14.7	<0.0001
LV-ESVI (ml/m^2)	58.1 ± 17.4	122.9 ± 40.4	<0.0001	107.2 ± 45.7	30.5 ± 8.0	<0.0001
LV-SVI (ml/m^2)	48.3 ± 18.4	35.2 ± 11.2	<0.0001	38.5 ± 14.5	42.8 ± 9.5	0.08
CI (l/min/m^2)	2.9 ± 0.8	2.7 ± 1.0	0.2	2.7 ± 0.9	2.9 ± 0.6	0.3
LV-EDD (mm)	63.6 ± 7.4	70.5 ± 7.7	0.0001	68.8 ± 8.2	50.8 ± 5.4	<0.0001
LVRI (g/ml)	0.8 ± 0.2	0.7 ± 0.2	0.05	0.7 ± 0.2	0.9 ± 0.2	<0.0001
RV-EDD (ml)	46.6 ± 6.2	43.5 ± 8.1	0.06	44.3 ± 7.7	43.2 ± 5.6	0.4
RAD (mm)	48.6 ± 8.9	48.4 ± 8.1	0.9	48.4 ± 8.3	43.8 ± 5.9	0.001
RVF (%)	49.1 ± 11.8	31.9 ± 16.8	<0.0001	36.2 ± 17.4	56.4 ± 6.3	<0.0001
RV-EDVI (ml/m^2)	85.4 ± 13.2	110.8 ± 41.1	0.002	104.4 ± 37.8	85.1 ± 9.4	0.001
RV-ESVI (ml/m^2)	40.6 ± 15.9	78.3 ± 44.4	<0.0001	68.9 ± 42.5	40.8 ± 11.7	<0.0001
RV-SVI (ml/m^2)	44.5 ± 9.7	34.6 ± 10.5	<0.0001	37.1 ± 11.2	42.5 ± 5.9	0.004
Presence of LGE	3/21 (14%)	21/56 (38%)	0.09	24/77 (31%)	–	–
% LGE Extent	4.8% (2.8–6.9 %)	8.3% (6.9–12.5 %)	0.2	8.3% (5.6–11.5 %)	–	–
EAT volume (ml)	50.0 ± 21.9	50.2 ± 13.9	0.9	50.2 ± 16.2	66.0 ± 15.3	<0.0001
indexed EAT volume (ml/m^2)	25.0 ± 10.4	25.7 ± 7.0	0.7	25.5 ± 8.0	33.5 ± 6.4	<0.0001
EAT mass (g)	47.0 ± 20.6	47.2 ± 13.1	0.9	47.2 ± 15.2	62.1 ± 14.4	<0.0001
indexed EAT mass (g/m^2)	23.5 ± 9.8	24.2 ± 6.6	0.7	24.0 ± 7.5	31.7 ± 5.6	<0.0001
EAT/LV mass ratio	0.3 ± 0.1	0.23 ± 0.1	0.001	0.24 ± 0.1	0.5 ± 0.1	<0.0001
EAT/LV volume ratio	0.3 ± 0.5	0.16 ± 0.1	0.005	0.20 ± 0.3	0.45 ± 0.1	<0.0001

$P^¥$-value comparing all patients with DCM and healthy controls, P^*-value comparing DCM patients with moderate and severe LV dysfunction

DCM irrespective of LV function impairment showed significantly increased LV mass, volume, and dimensions, compared to healthy controls.

Patients with DCM revealed significantly decreased EAT mass compared to healthy controls. There was a significant correlation between EAT mass and LV volume, LV diameter, and LV mass in patients with DCM. However, the EAT mass did not correlate with the degree of LV function impairment. Previous studies (32,33) have shown that the development of LVH appears to have protective and beneficial effects in patients with DCM by reducing systemic wall stress and protecting against further dilatation of the LV. In our study cohort, patients with eccentric LVH showed significantly elevated EAT mass compared to DCM patients without LVH. However, compared to healthy controls, the EAT mass was less even in patients with LVH. The fact that the EAT mass in patients with DCM was unaffected of the presence of arterial hypertension makes a direct influence of arterial hypertension on the EAT mass unlikely. Nevertheless, whether the increased EAT mass is solely explained by the increase of EAT in line with the increase in LV mass as discussed in previous studies (34,35) cannot be distinguished.

Since the presence of LGE has a prognostic implication in patients with DCM (22,36), we analyzed the presence of LGE with regard to EAT mass. In our study cohort, 24/77 (31%) exhibited LGE. In the DCM patients with LGE, the EAT mass was slightly but not statistically significant higher compared to those without LGE. However, due to the small number of patients in the subgroup analysis, our study might be underpowered for this analysis.

Interestingly, EAT mass did not correlate with the degree of LV function impairment. Subgroup analysis in DCM patients according to LV function showed an indexed EAT mass of 24.2 ± 6.6 g/m^2 in the 84 DCM patients with severely reduced LVF (≤35%). This result was comparable to the previously reported EAT mass in these patients (9,10). In the 28 DCM patients with only moderate LV dysfunction (LVF >35%), indexed EAT mass was equally diminished (23.5 ± 9.8 g/m^2). In addition to that, linear regression analysis revealed no correlation between EAT mass and LV function impairment. In this context, Khawaja et al. (11) using cardiac CT examined the relation of EAT volume in patients with normal and impaired LV function referred to myocardial perfusion scanning for assessment of CAD. The patients with normal LVF served as a control group. Heart failure was defined by LVF <55%. Similarly to our findings, a significantly reduced EAT volume was found in patients with reduced LVF (LVF <55%) compared to patients with normal LVF. However, in the subgroup analysis, EAT volume showed a statistically significant stepwise decrease in EAT volume in the moderate heart failure (EF 35-55%), which decreased further in the severe heart failure group (EF <35%). Thus, contrary to our

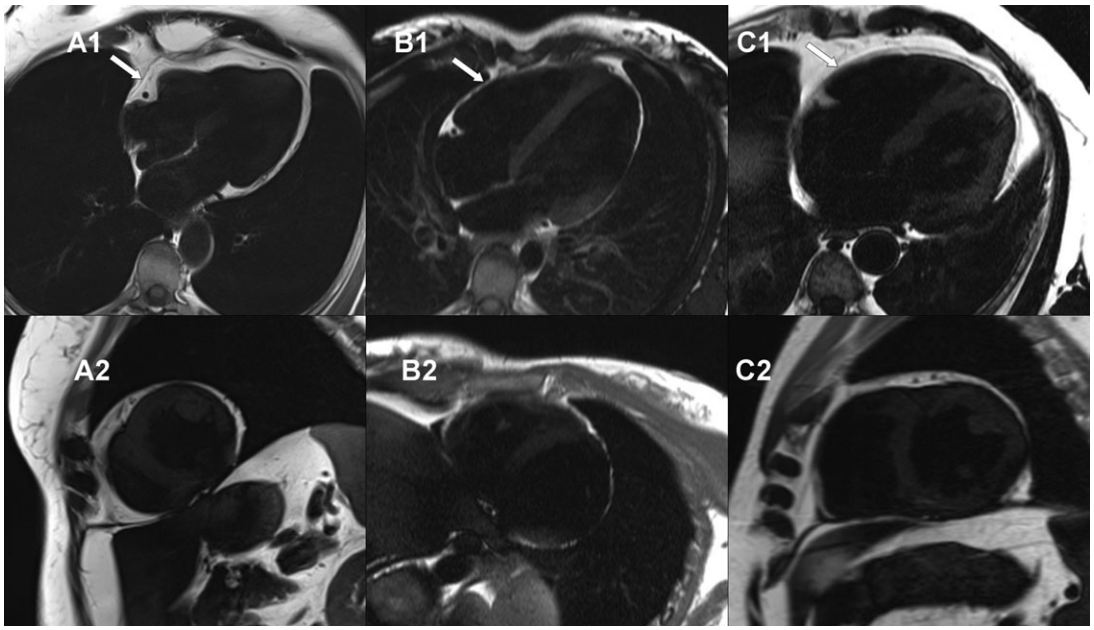

FIGURE 1 The upper panel shows the four chamber view of a healthy control (A1) and patients with moderately reduced LVF (B1) and severely reduced LVF (C1). The epicardial adipose tissue (EAT) is indicated by the white arrows. The lower panel shows the respective short-axis views. Compared to healthy controls (A1/2), patients with DCM and moderately (B1/2) and severely (C1/2) reduced left ventricular ejection fraction showed equally diminished indexed EAT mass.

TABLE 3 Correlation of patient characteristics and CMR parameters with indexed EAT

	All patients with DCM ($n = 112$)		Healthy controls ($n = 48$)	
	r/z	*P*	*r/z*	*P*
Age (years)	0.166	0.08	0.461	0.001
Male Sex	-2.093	0.04	−0.932	0.4
BMI (kg/m^2)	0.003	0.98	0.426	0.003
LVF (%)	0.085	0.37	0.069	0.6
LV-EDMI (g/m^2)	0.417	<0.0001	0.346	0.02
LV-EDVI (ml/m^2)	0.251	0.01	0.007	0.96
LV-ESVI (ml/m^2)	0.239	0.01	0.0001	0.99
LV-SVI (ml/m^2)	0.141	0.1	0.018	0.9
CI (l/min/m^2)	0.123	0.2	0.259	0.08
LV-EDD (mm)	0.220	0.02	0.014	0.9
LVRI (g/ml)	0.116	0.2	0.204	0.2
RVF (%)	0.049	0.6	0.169	0.3
RV-EDVI (ml/m^2)	0.186	0.05	0.153	0.3
RV-ESVI (ml/m^2)	0.156	0.1	0.171	0.2
RV-EDD (ml)	0.093	0.3	0.127	0.4
RAD (mm)	0.080	0.4	0.136	0.4
Presence of LGE[a]	-1.501	0.1	–	–
LGE[a] extent %	0.189	0.1	–	–

[a]Presence of LGE studied in 77 DCM patients*CI: cardiac index,*

findings, the results by Khawaja et al. (11) indicate a correlation of smaller EAT volumes with the degree of LVF impairment. These discrepant results are due to the difference in the examined study population and control group. In the present study, the cohort consisted solely of patients with DCM, and only healthy subjects served as a control group. Whereas the study population and the controls of Khawaja et al. (11) were heterogeneous and included mainly patients with HF due to ischemic cardiomyopathy (ICM). Since patients with ICM and DCM show a different course of LV remodeling, one could assume that the relation of EAT amount and the LVF is yet not irrespective of the underlying etiology. In patients with heart failure, severely reduced LVF (<35%) and significant LV cavity dilation, representing the end stage of the disease course, the amount of EAT seems to be reduced irrespective of the underlying etiology as we already showed (9,10). However, we suspect that this does not hold true for the whole spectrum of LV function impairment.

We found that in patients with DCM, the amount of EAT is significantly reduced compared to healthy controls irrespective of the LV function impairment. LV remodeling coming along with an increase in LV diameter and volumes as well as LV mass seems to play a major role in the EAT changes in patients with DCM.

We speculate that with increasing LV dilatation, there is a suppression of EAT. The decrease of the EAT mass coming along with LV remodeling may result in a discontinuation of its protective effects on the heart. This may contribute in an undernourishment of the adjacent myocytes, especially under conditions of special energy demand inducing a vicious circle with a further progressive EAT reduction.

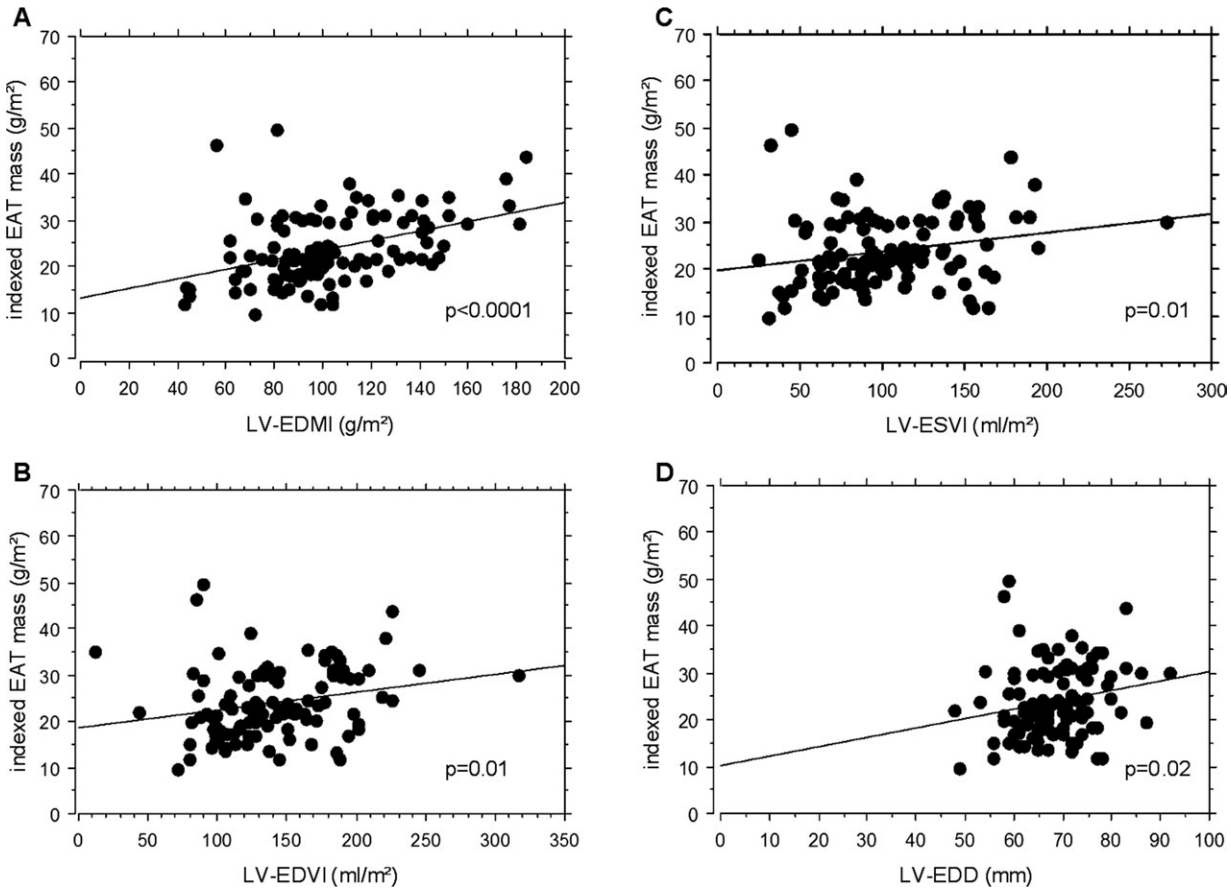

FIGURE 2 Regression plots illustrating the relationship between indexed EAT (g/m^2) and LV-EDMI (g/m^2) (2A), LV-EDVI (ml/m^2) (2B), LV-ESVI (ml/m^2) (2C), and LV-EDD (mm) (2D) in patients with DCM.

Although our DCM patients with severely impaired LVF $\leq$ 35% received, due to standard heart failure treatment, significantly more ACE/ARB, diuretics, and digoxin than those with LVF >35%, we do not believe that the medication has a direct effect on EAT. This assumption is supported by the fact that the EAT mass 24.2 $\pm$ 6.6 g/m^2 in the 84 patients with severely reduced LVF ($\leq$35%) was comparable to those in the 28 patients with only moderate (LVF>35) 23.5 $\pm$ 9.8 g/m^2. However, we believe that medication has an indirect effect on EAT in patients with DCM. Since in patients with DCM, EAT mass showed a significant correlation with LV volume, LV diameter, and LV mass, medications influencing cardiac remodeling consequently may also have an indirect effect on EAT.

Larger study cohorts with homogeneous study populations are needed to further prove the potential different interactions between LVF and EAT in different causes of HF.

Study limitations

The diagnosis of DCM was based solely on clinical history and examination accompanied by echocardiography and normal findings at CA. In line with the current guidelines (37), none of the patients underwent myocardial biopsy for the diagnosis of DCM, since myocardial biopsy is limited by the possibility of false-negative results and is associated with a significant clinical risk (38,39).

To date, there is no accepted method for the calculation of EAT with either CT or CMR. Magnetic resonance imaging is recognized as the ''gold standard'' modality for imaging adipose tissue (18,40,41). However, CMR has only recently evolved to assess adiposity around the heart (19). In a previous study of our group, we introduced a new volumetric method for the assessment of EAT (19), tracing the EAT from the level of the mitral valve to its most inferior margin. However, this methodology hasn't been verified against actual measurement of *ex vivo* mass. In the study by Nelson et al. (18), this method was applied to measure the paracardial adipose tissue with CMR and to correlate these results with ex vivo paracardial adipose tissue mass in 11 merino sheep. The authors could show that the CMR-derived paracardial adipose tissue accurately reflected ex vivo paracardial adipose tissue mass. One could assume that these results also hold true for EAT measurements.

Furthermore, using this approach, we do not include EAT surrounding the atria and the whole perivascular EAT amount. However, it is known that only minor foci of EAT are found around the atria, and therefore, their contribution to total EAT is known to be minor (24).O

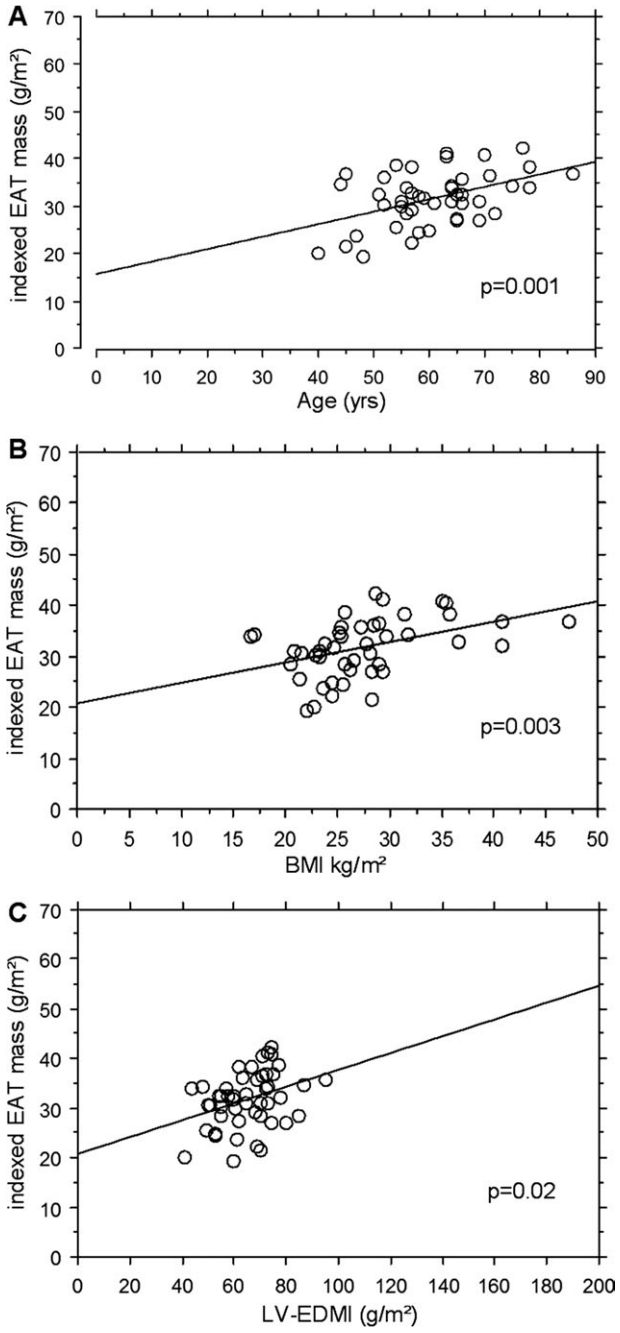

FIGURE 3 Regression plots showing the relationship between indexed EAT (g/m^2) and age (years) (3A), BMI (kg/m^2) (3B), and LV-EDMI (g/m^2) (3C) in healthy controls.

Conclusion

This is the first study to evaluate the association between the amount of EAT and CMR parameters of ventricular remodeling in patients with different degrees of LV function impairment compared to age-matched controls. We found that in patients with DCM the amount of EAT is significantly reduced compared to healthy controls irrespective of the LV function impairment. LV remodeling coming along with an increase in LV diameter and volumes as well as LV mass seems to play a major role in the EAT changes in patients with DCM.

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