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ORIGINAL ARTICLE

Impact of epicardial adipose tissue on cardiac function and morphology in patients with diastolic dysfunction

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Abstract

Aims This study aimed to identify the impact of increased epicardial adipose tissue (EAT) and its regional distribution on cardiac function in patients with diastolic dysfunction.

Methods and results Sixty-eight patients with exertional dyspnoea (New York Heart Association ≥II), preserved ejection fraction (≥50%), and diastolic dysfunction (E/e' ≥ 8) underwent rest and stress right heart catheterization, transthoracic echocardiography, and cardiovascular magnetic resonance (CMR). EAT volumes were depicted from CMR short-axis stacks. First, the impact of increased EAT above the median was investigated. Second, the association of ventricular and atrial EAT with myocardial deformation at rest and during exercise stress was analysed in a multivariable regression analysis. Patients with high EAT had higher HFA-PEFF and H2FPEFF scores as well as N-terminal prohormone of brain natriuretic peptide levels (all $P < 0.048$). They were diagnosed with manifest heart failure with preserved ejection fraction (HFpEF) more frequently (low EAT: 37% vs. high EAT: 64%; $P = 0.029$) and had signs of adverse remodelling indicated by higher T1 times ($P < 0.001$). No differences in biventricular volumetry and left ventricular mass (all $P > 0.074$) were observed. Patients with high EAT had impaired atrial strain at rest and during exercise stress, and impaired ventricular strain during exercise stress. Regionally increased EAT was independently associated with functional impairment of the adjacent chambers.

Conclusions Patients with diastolic dysfunction and increased EAT show more pronounced signs of diastolic functional failure and adverse structural remodelling. Despite similar morphological characteristics, patients with high EAT show significant cardiac functional impairment, in particular in the atria. Our results indicate that regionally increased EAT directly induces atrial functional failure, which represents a distinct pathophysiological feature in HFpEF.

Keywords Diastolic dysfunction; HFpEF; Epicardial fat; Cardiovascular magnetic resonance; Cardiac function

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Introduction

Epicardial adipose tissue (EAT) has emerged as an important risk factor in multiple diseases, while it seems to accelerate cardiac functional deterioration and increase the probability of adverse events.[1-4] Studies revealed that patients with increased EAT show haemodynamic alterations with functional impairment of both ventricles, as well as increased cardiac filling pressures at rest and during exercise stress with concomitantly reduced exercise capacity.[5-8] Furthermore, EAT directly impacts local cardiac structure[4] and is suspected to cause inflammation and remodelling, both playing a role in the development and progression of cardiovascular disease.[9-11]

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The subsequent cardiac remodelling was observed to induce typical pathophysiological and morphological conditions observed in patients with diastolic dysfunction and heart failure with preserved ejection fraction (HFpEF).[5,12] This risk for diastolic dysfunction due to increased EAT volume was found to be present in early adolescence and otherwise healthy individuals.[13,14]

Albeit those first findings offering an enhanced understanding of the pathogenesis of diastolic dysfunction and HFpEF, a detailed exploration of the implications of regional epicardial fat on the function of the associated cardiac chambers is lacking.

We hypothesized that the total amount and the distribution of EAT around distinct myocardial regions within patients with diastolic dysfunction would contribute to more severe functional impairment and structural changes.

Methods

Patient cohort

Sixty-eight patients with dyspnoea at exertion [New York Heart Association (NYHA) ≥II], preserved ejection fraction (EF) (≥50%), and signs of diastolic dysfunction (E/e' ≥ 8) were recruited after initial referral for echocardiographic evaluation of dyspnoea within the HFpEF-Stress trial.[15] During screening, exclusion criteria comprised other causes of dyspnoea including pulmonary disease identified on spirometry (FEV1 < 80%), coronary artery disease, or cardiovascular disease including cardiomyopathies, ischaemic, non-ischaemic, or valvular heart diseases, as well as typical contraindications for cardiovascular magnetic resonance (CMR).[15] Patients were diagnosed with HFpEF according to thresholds of pulmonary capillary wedge pressure (PCWP) ≥15 mmHg at rest or ≥25 mmHg during exercise stress right heart catheterization (RHC).[16] Rest and stress echocardiographic assessments were conducted simultaneously to RHC and followed by a CMR within 24 h.[15]

Right heart catheterization and echocardiographic assessments

Using a standardized 5-W-increasing exercise ramp protocol on a bicycle ergometer in supine position, patients had to achieve and maintain heart rates between 100 and 110 b.p.m.[15,17]

Assessments of pulmonary artery (PA) pressure, PCWP, cardiac index (CI), and pulmonary vascular resistance were conducted during RHC.

Simultaneously to RHC, transthoracic echocardiographic assessments at rest and during exercise stress comprised measurements in apical long-axis (LAX) and parasternal short-axis (SAX) views.[15] Ventricular and atrial dimensions were obtained, as well as functional parameters for systolic and diastolic function using appropriate techniques such as M-mode, pulsed-wave, and continuous-wave Doppler as suggested by current guidelines.[16] Global longitudinal strain (GLS) at rest and during exercise stress was measured by echocardiographic speckle tracking of the left ventricle in longitudinal two-, three-, and four-chamber views.[15]

Cardiovascular magnetic resonance

CMR images were obtained on a 3.0 T MAGNETOM Skyra (Siemens Healthcare, Erlangen, Germany) using a 32-channel cardiac surface receiver coil. For post-processing, a commercially available software was used (Medis, QMass®, Medical Imaging Systems, Leiden, The Netherlands).[18]

During the CMR survey, patients were exposed to exercise stress using the same ramp protocol as for RHC before on a CMR-compatible supine ergometer (Lode, Leiden, The Netherlands).

Volumetric measures were obtained from balanced steady-state free precession (bSSFP) cine-sequence SAX stacks with full coverage of the atria and ventricles [25 frames per cardiac cycle, echo time (TE) of 1.5 ms, repetition time (TR) of 55 ms, flip angle of 55°, and slice thickness of 7 mm with a 7.7 mm inter-slice gap].

Real-time (RT) images at rest and during exercise stress were acquired using heavily under-sampled bSSFP sequences and iterative reconstruction as described by Uecker *et al*.[19]

Manual LAX strains for all four chambers (left atrium/left ventricle/right atrium/right ventricle) of the heart were assessed using OsiriX MD (Pixmeo SARL, Bernex, Switzerland).[15]

For T1 measurements, a septal region of interest (ROI) was manually delineated in a single midventricular SAX slice obtained using a 5(3)3 Modified Look-Locker Inversion Recovery sequence [field of view (FOV) of 360 × 306.6 mm^2, in-plane resolution of 1.41 × 1.41 × 8 mm^3, TR of 280 ms, TE of 1.12 ms, inversion time (TI) of 180 ms, flip angle of 35°, and bandwidth of 1085 Hz/pixel with total acquisition of 11 heart beats].[20]

Calculation of epicardial adipose tissue

EAT volume was calculated as previously proposed and validated.[1,5] Prior to the quantification of EAT volumes, the presence of EAT was validated in pre-contrast and post-contrast T1 maps. Hereby, T1 times of subcutaneous fat and suspected epicardial fat were compared by manually drawn ROIs. EAT was defined as the adipose tissue between the outer layer of the myocardium and the visceral layer of the pericardium and

manually delineated in end-diastolic SAX slices from the most basal slice around the atria up to the apical slices of the ventricle (cf. *Figure 1*). The localization of the mitral valve was used to differentiate between atrial and ventricular EAT. The total EAT volume per patient was computed by the modified Simpson rule.[21]

The calculation of EAT was performed blinded to patient characteristics and other functional and morphological results.

Statistical analysis

All statistical analyses were performed using SPSS Version 28 (IBM, Armonk, NY, USA) and GraphPad Prism 9 (GraphPad Software, CA, USA). A Shapiro–Wilk test was used to test for normal distribution. Categorical variables are displayed as frequencies and percentages and were compared by the χ^2 test. Continuous variables are shown as median with corresponding inter-quartile ranges (IQRs) and were compared using the nonparametric Mann–Whitney *U* test.

Associations between markers for diastolic dysfunction and EAT were tested with multiple univariable linear regressions. PCWP and E/e' as conventional diastolic functional parameters and the CMR-derived long axial strain (LAS) of all four individual chambers at rest and during exercise stress were tested for association with total and regional EAT using a multivariable linear regression analysis. Patient-specific characteristics and risk factors potentially influencing the presence of EAT [age, sex, body mass index (BMI), hyperlipoproteinaemia (HLP), and diabetes] were included in the analysis. In categorical variables, association was tested for the presence of HLP, the presence of diabetes, and male sex. *P* values below 0.05 were considered statistically significant.

Results

Baseline characteristics

For further assessments, the cohort was dichotomized at the median of the total EAT volume for comparisons between the groups with high EAT ($>$60.7 mL/m^2) and low EAT ($\leq$60.7 mL/m^2) (cf. *Figure 2*).

Figure 1 Delineation of epicardial adipose tissue (EAT). The segmentation of atrial EAT in a four-chamber view (A) and short-axis stack (B). The segmentation of ventricular EAT in a four-chamber view (C) and short-axis stack (D).

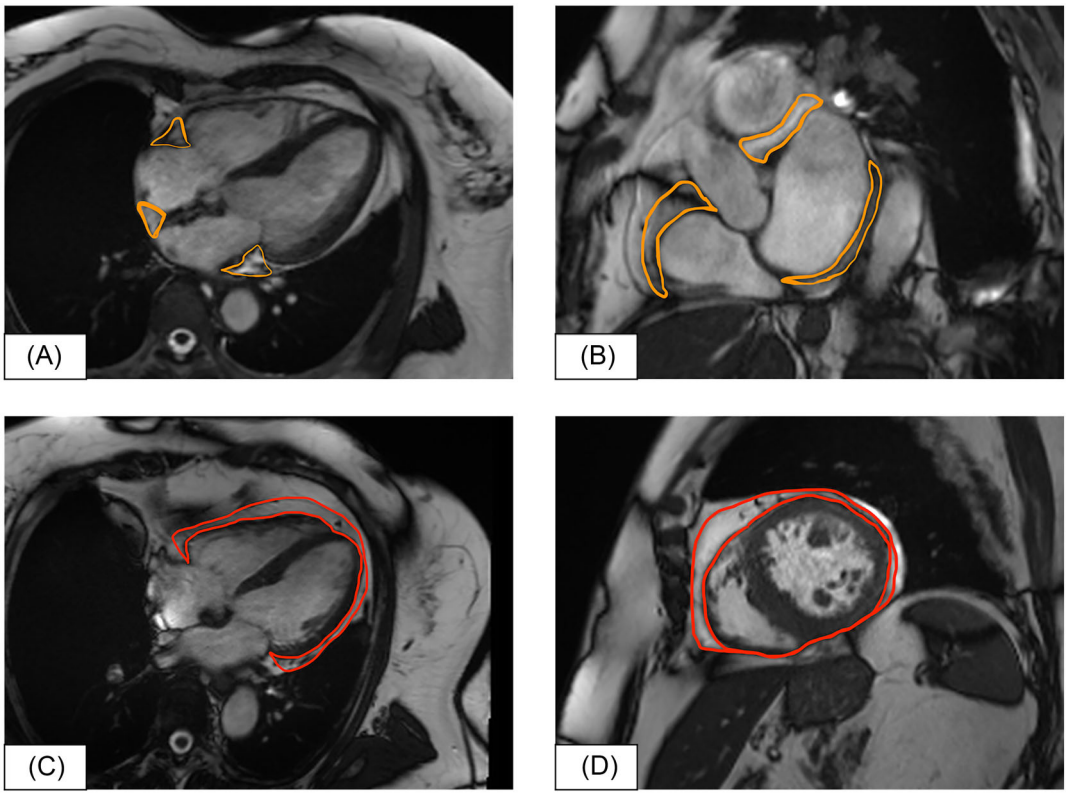


Figure 2 Main findings in patients with increased epicardial adipose tissue (EAT) volumes. The patient cohort was dichotomized into patients with low and high EAT volumes. Patients with high EAT volumes revealed specific morphological and functional characteristics as diagnosed by right heart catheterization (RHC) and cardiovascular magnetic resonance (CMR). HFpEF, heart failure with preserved ejection fraction; LV, left ventricular.

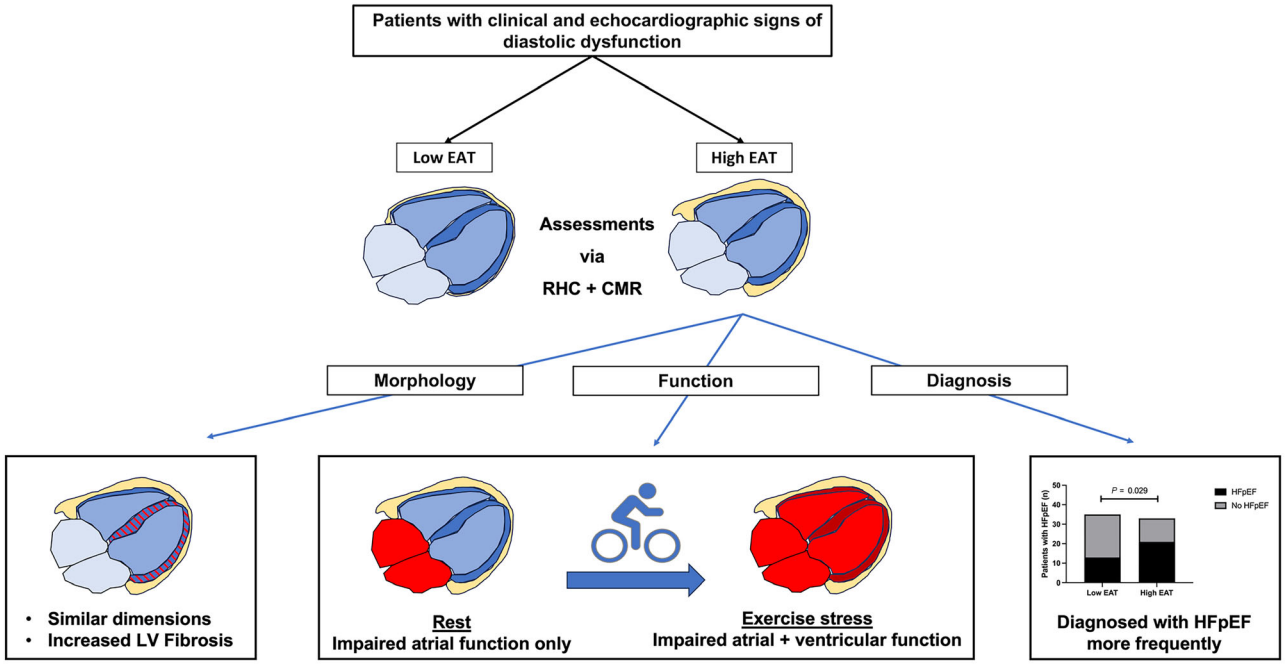


Table 1 Baseline characteristics

Parameter	Low EAT (n = 35)	High EAT (n = 33)	P value
Age (years)	68 (60–73)	69 (66–73)	0.256
BMI (kg/m^2 BSA)	27.5 (26.1–33.2)	28.4 (26.9–32.8)	0.384
NYHA (II/III)	25/10	23/10	0.867
Female	21 (60)	23 (70)	0.403
Diabetes, n (%)	4 (11)	6 (18)	0.432
AHT, n (%)	27 (77)	27 (82)	0.634
AF, n (%)	7 (20)	14 (42)	0.045*
HLP, n (%)	19 (54)	23 (70)	0.191
Smoking, n (%)	3 (9)	6 (18)	0.242
HFA-PEFF score	3 (2–5)	4 (4–6)	0.004*
H2FPEFF score	3 (2–5)	5 (3–6)	0.017*
HFpEF, n (%)	13 (37)	21 (64)	0.029*

AF, atrial fibrillation; AHT, arterial hypertension; BMI, body mass index; BSA, body surface area; EAT, epicardial adipose tissue; H2FPEFF score, body mass index >30 kg/m^2, ≥2 antihypertensive drugs, atrial fibrillation, pulmonary artery systolic pressure >35 mmHg, >60 years, and E/e' > 9; HFA-PEFF score, Heart Failure Association diagnostic algorithm score; HFpEF, heart failure with preserved ejection fraction; HLP, hyperlipoproteinaemia; NYHA, New York Heart Association class.
Patient baseline characteristics after dichotomization at the median of 60.7 mL/m^2 total EAT.
*P values below 0.05 were considered statistically significant.

Baseline characteristics can be appreciated from *Table 1*. Patients with increased EAT volumes had a higher prevalence of atrial fibrillation (P = 0.045) and revealed higher HFA-PEFF and H2FPEFF scores (HFA-PEFF: 3 vs. 4; P = 0.004 and H2FPEFF: 3 vs. 5; P = 0.017). Furthermore, patients with high EAT volumes were diagnosed with manifest HFpEF more frequently using thresholds of RHC (low EAT: 37% vs. high EAT: 64%; P = 0.029) (see *Figure 2*).

Impact of increased total epicardial adipose tissue on laboratory markers, functional and structural parameters by right heart catheterization, echocardiography, and cardiovascular magnetic resonance

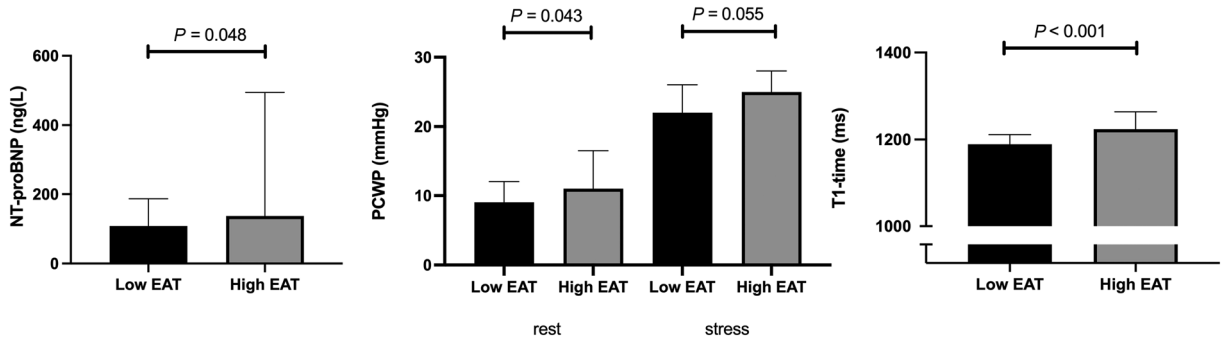
As presented in *Table 2* and *Figure 3*, patients with higher EAT volume had increased levels of the N-terminal

Table 2 Laboratory markers, echocardiography, and right heart catheterization

Parameter	Low EAT (n = 35)	High EAT (n = 33)	P value
Laboratory markers			
NT-proBNP (ng/L)	107.5 (58.1–186.5)	136.6 (77.2–495.0)	0.048*
Creatinine (mg/dL)	0.9 (0.8–1.0)	0.8 (0.7–1.0)	0.461
hsCRP (mg/L)	1.49 (0.67–2.71)	1.48 (0.81–4.2)	0.318
Echocardiography			
E/e′ rest	10.4 (8.2–12.5)	10.8 (9.3–13.0)	0.124
E/e′ stress	12.0 (10.0–14.4)	13.8 (10.3–16.3)	0.449
LAVI (mL/m^2)	37.5 (28.4–50.3)	38.5 (36.1–47.4)	0.311
PAPsys (mmHg)	23.9 (21.0–28.0)	24.8 (21.6–33.0)	0.380
LV-GLS rest (%)	−15.9 (−19.8 to −13.3)	−15.4 (−18.2 to −12.2)	0.345
LV-GLS stress (%)	−14.9 (−19.6 to −12.7)	−15.6 (−17.3 to −13.6)	1.0
Right heart catheterization			
PCWP rest (mmHg)	9.0 (7.0–12.0)	11.0 (10.0–16.5)	0.043*
PCWP stress (mmHg)	22.0 (13.0–26.0)	25.0 (19.5–28.0)	0.055
PA rest (mmHg)	19.0 (16.0–21.0)	20.0 (17.0–24.5)	0.091
PA stress (mmHg)	36.0 (26.0–42.0)	42.0 (36.5–47.0)	0.005*
CI rest (L/m^2 BSA)	3.0 (2.7–3.6)	2.7 (2.4–3.0)	0.017*
CI stress (L/m^2 BSA)	5.6 (4.8–6.5)	5.1 (4.0–6.1)	0.078
PVR rest (Wood units)	1.5 (1.1–1.8)	1.7 (1.2–2.5)	0.130
PVR stress (Wood units)	1.3 (1.1–1.7)	1.7 (1.3–2.5)	0.030*

BSA, body surface area; CI, cardiac index; E, passive mitral inflow; e′, septal and lateral mitral annulus velocity; EAT, epicardial adipose tissue; GLS, global longitudinal strain; hsCRP, high-sensitivity C-reactive protein; LAVI, left atrial volume index; LV, left ventricular; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; PA, pulmonary artery; PAPsys, pulmonary artery systolic pressure; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance.
Laboratory markers, echocardiography, and right heart catheterization assessments of the patients after dichotomization at the median of 60.7 mL/m^2 total EAT.
*P values below 0.05 were considered statistically significant.

Figure 3 Comparison of N-terminal prohormone of brain natriuretic peptide (NT-proBNP), pulmonary capillary wedge pressure (PCWP), and T1 times within patients with high and low epicardial adipose tissue (EAT). Displayed are the median NT-proBNP, PCWP, and T1 times with inter-quartile ranges within patients with high EAT (>60.7 mL/m^2) and low EAT (<60.7 mL/m^2). P values below 0.05 were considered statistically significant.



prohormone of brain natriuretic peptide (NT-proBNP) (P = 0.048), while echocardiographic measurements did not reveal significant differences between both groups ($P > 0.124$).

During RHC, patients with increased EAT volume had increased PCWP at rest (P = 0.043) with the same trend for PCWP during stress (P = 0.055) (see *Figure 3*). Additionally, they revealed concordantly increased PA pressure during exercise stress in particular (P = 0.005) paired with a higher pulmonary vascular resistance (P = 0.030). The total cardiac output was reduced in the high EAT volume group at rest (P = 0.017) with the same trend for the CI during exercise stress (P = 0.078). Detailed results can be obtained from *Table 2*.

As measured in CMR, in patients with increased total EAT volume, no difference in right ventricular (RV) and left ventricular (LV) end-diastolic volume (EDV) and end-systolic volume (ESV), as well as LV mass, could be observed (all $P > 0.074$) compared with patients with lower EAT volumes (see *Figure 2* and *Table 3*).

In the high EAT volume group, ventricular strain of the right ventricle and the left ventricle was impaired during exercise stress (right ventricle: P = 0.006; left ventricle: P = 0.002) but not at rest (right ventricle: P = 0.372; left ventricle: P = 0.089).

Meanwhile, strain of the right atrium and left atrium was impaired at rest already (right atrium: P = 0.002; left atrium: P = 0.016) and remained lower during exercise stress

Table 3 Cardiovascular magnetic resonance imaging

Parameter	Low EAT (n = 35)	High EAT (n = 33)	P value
Left ventricle			
LV mass (g/m^2 BSA)	55.6 (50.7–71.4)	58.1 (50.7–68.1)	0.878
LV EDV (mL/m^2 BSA)	72.4 (61.1–78.6)	65.0 (56.3–74.0)	0.074
LV ESV (mL/m^2 BSA)	20.1 (16.4–26.4)	20.3 (14.1–24.8)	0.439
LVEF (%)	69.3 (66.1–75.9)	68.6 (65.1–76.3)	0.985
LV SV (mL/m^2 BSA)	51.3 (43.2–56.0)	45.0 (40.6–51.9)	0.041*
LV LAS rest (%)	14.2 (11.7–16.7)	13.7 (11.7–14.8)	0.089
LV LAS stress (%)	18.7 (15.3–21.6)	15.6 (12.7–18.3)	0.002*
T1 time (ms)	1189 (1167–1211)	1224 (1196–1264)	<0.001*
Right ventricle			
RV EDV (mL/m^2 BSA)	67.8 (58.5–75.8)	62.5 (53.7–69.6)	0.133
RV ESV (mL/m^2 BSA)	22.8 (18.8–28.2)	20.6 (16.3–25.7)	0.175
RV SV (mL/m^2 BSA)	44.0 (39.0–51.8)	42.4 (36.4–48.9)	0.390
RV EF (%)	64.8 (62.2–68.4)	66.7 (59.6–71.7)	0.540
RV LAS rest (%)	26.0 (21.8–27.5)	24.6 (20.1–28.7)	0.372
RV LAS stress (%)	28.8 (25.6–31.4)	24.8 (20.3–28.7)	0.006*
Left atrium			
LAVI (mL/m^2 BSA)	42.7 (29.7–54.0)	41.0 (33.2–51.3)	0.830
LA LAS rest (%)	21.6 (17.2–26.6)	16.9 (13.1–21.5)	0.016*
LA LAS stress (%)	25.9 (18.9–31.5)	18.4 (13.8–27.0)	0.006*
Right atrium			
RAVI (mL/m^2 BSA)	47.4 (40.0–61.6)	48.1 (40.5–55.7)	0.969
RA LAS rest (%)	31.0 (28.2–35.4)	24.7 (21.9–31.0)	0.002*
RA LAS stress (%)	37.0 (30.3–41.5)	32.0 (26.0–37.6)	0.032*

BSA, body surface area; CMR, cardiovascular magnetic resonance; EAT, epicardial adipose tissue; EDV, end-diastolic volume; EF, ejection fraction; ESV, end-systolic volume; LA, left atrial; LAS, long axial strain; LAVI, left atrial volume index; LV, left ventricular; LVEF, left ventricular ejection fraction; RA, right atrial; RAVI, right atrial volume index; RV, right ventricular; SV, stroke volume.
Comprehensive CMR of patients after dichotomization at the median of 60.7 mL/m^2 total EAT.
*P values below 0.05 were considered statistically significant.

in patients with high EAT volumes (right atrium: P = 0.032; left atrium: P = 0.006).

Patients with higher EAT volumes had signs of increased myocardial fibrosis as indicated by longer T1 times ($P < 0.001$) (see *Figure 3*). The detailed results of the CMR analysis can be depicted in *Table 3*.

Association of total, atrial, and ventricular epicardial adipose tissue with diastolic functional parameters and regional cardiac strain in cardiovascular magnetic resonance

EAT was majorly located in front of the ventricles compared with the atria (44.9 vs. 16.8 mL/m^2; $P < 0.001$) (cf. *Figure 4*).

In multivariable regression analysis, increasing total EAT volume was independently associated with higher PCWP during exercise stress (P = 0.029) but not at rest (P = 0.310). For echocardiography, increasing total EAT volume showed a trend towards higher E/e' at rest (P = 0.081), but no association was found during exercise stress (P = 0.593) (see *Table 4*). Furthermore, increasing total EAT volume was independently associated with impaired LV and left atrial (LA) LAS at rest and during exercise stress (all $P < 0.039$). RV LAS only revealed an association with total EAT volume during exercise stress, while impaired right atrial (RA) LAS was associated with higher total EAT volume at rest ($P < 0.001$) and showed a strong trend for an association during exercise stress (P = 0.050) (cf. *Table 5*).

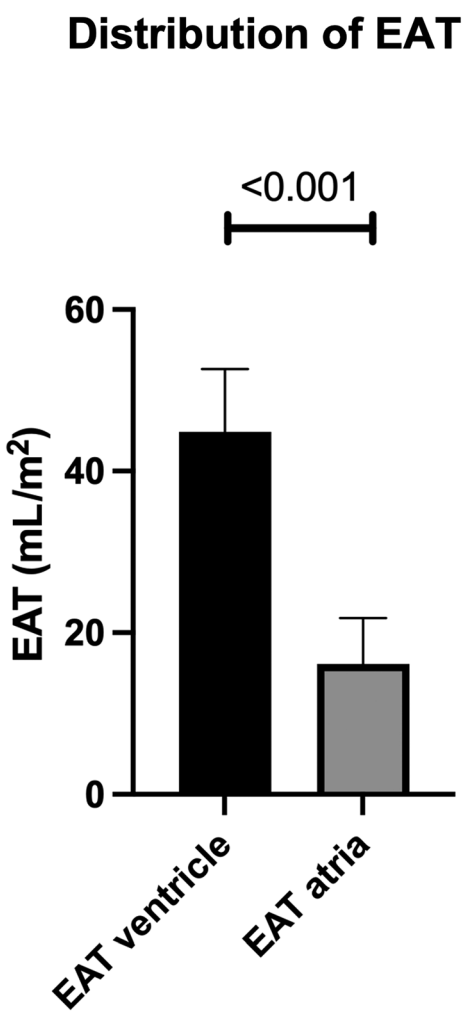
For regional EAT, increasing ventricular EAT volume was independently associated with impaired LV strain at rest and during exercise stress ($P < 0.023$). Meanwhile, in the right ventricle, higher ventricular EAT volume was independently associated with decreasing RV LAS during exercise stress only (P = 0.042) (see *Table 5*). In turn, atrial EAT volume was independently associated with decreasing atrial strain at rest and during exercise stress ($P < 0.027$), besides for RA LAS during exercise stress (0.118) (see *Table 5*).

Discussion

Numerous studies have identified EAT as an important risk factor in cardiovascular disease,[2,3,5] while it promotes the development of diastolic dysfunction and HFpEF.[8] This study was now able to show that patients with preexisting diastolic dysfunction and increased EAT volume show pronounced signs of diastolic failure and adverse remodelling. Despite similar morphological characteristics, functional impairment is stronger in patients with higher EAT volumes. In particular, atrial function is impaired to a higher degree than ventricular cardiac function, and regional EAT in front of the ventricles and atria is independently associated with the functional impairment of the associated cardiac chambers. Those results strengthen the need for a more detailed classification and characterization of patients with diastolic dysfunction, as distinct phenotypes might require different handling.

Cardiac dyspnoea is mostly caused by pulmonary congestion due to compromised cardiac output by either reduced ejection or reduced filling. EAT was associated with diastolic dysfunction but not with systolic functional impairment in multiple studies.[22,23] The underlying pathomechanisms comprise two interacting theories. On the one hand, EAT restricts the heart in its function and particularly diminishes diastolic relaxation capacities such as commonly observed in pericardial effusion.[24] On the other hand, EAT is known to induce myocardial inflammation, either by migration of fat tissue from the epicardium directly into the myocardium or by proinflammatory mediators of fat tissue in direct regional relation to the myocardium.[24] The inflammatory processes are often followed by subsequent remodelling, which is mostly hypertrophic.[25]

Figure 4 Distribution of epicardial adipose tissue (EAT) in front of the ventricles and atria. Displayed is the median EAT with the inter-quartile range of the ventricles and the atria in the overall cohort.



Both described mechanisms, the restriction and the inflammation, impose typical conditions for diastolic dysfunction including higher filling pressures of the left ventricle hand in hand with a higher workload for ventricular filling and subsequent backward failure, which typically cause pulmonary congestion and dyspnoea.[26,27]

All patients in this cohort suffered from clinically apparent dyspnoea at exertion and incident echocardiographic signs of diastolic dysfunction. However, patients with higher volumes of EAT showed more pronounced signs of diastolic failure and higher rates of manifest HFpEF.

Despite significantly differing amounts of EAT volumes from around 20 to 120 mL/m^2 in other HFpEF study populations,[1,8] HFpEF patients with high EAT volume always had impaired haemodynamics, out of proportional exercise intolerance and worse outcomes compared with patients with low EAT volume.[1,7]

Importantly, at this stage, we could not observe differences in the ventricular volumetry and mass between the groups with high and low EAT volumes, whereas functional differences were already present.

Even though the conventional echocardiographic diastolic functional parameter E/e' did not reveal an association with increased EAT volumes, exercise stress PCWP as the reference standard of diastolic functional assessment showed an independent association with increasing EAT volumes, pointing out to a potential link of both pathologies. Furthermore, impaired LV and LA LAS as non-invasive CMR parameters, which were previously linked to the diagnosis of diastolic dysfunction and

Table 4 Multivariable regression analysis of the association of regional cardiac strain with total, ventricular, and atrial epicardial adipose tissue and patient characteristic in the overall cohort

	PCWP rest		PCWP stress		E/e' rest		E/e' stress	
	Standardized coefficient β	*P* value	Standardized coefficient β	*P* value	Standardized coefficient β	*P* value	Standardized coefficient β	*P* value
Total EAT	0.117	0.310	0.254	0.029*	0.206	0.081	0.078	0.593
Age	0.405	0.002*	0.409	0.002*	0.282	0.029*	0.095	0.552
BMI	0.449	<0.001*	0.269	0.030*	0.044	0.726	−0.198	0.209
Diabetes	0.001	0.996	0.047	0.684	−0.050	0.673	0.031	0.832
HLP	−0.004	0.973	−0.067	0.555	−0.048	0.682	−0.028	0.849
Sex	−0.010	0.932	−0.084	0.461	**−0.262**	0.026*	−0.261	0.078

BMI, body mass index; EAT, epicardial adipose tissue; HLP, hyperlipoproteinaemia; PCWP, pulmonary capillary wedge pressure.
Multivariable regression analysis of the association of PCWP and E/e' with total EAT and patient characteristics in the overall cohort. Data are presented as the standardized association coefficient β with referring *P* values.
**P* values below 0.05 were considered statistically significant.

Table 5 Multivariable regression analysis of the association of regional cardiac strain with total, ventricular, and atrial epicardial adipose tissue and patient characteristic in the overall cohort

	LV LAS rest		LV LAS stress		RV LAS rest		RV LAS stress	
Ventricles	Standardized coefficient β	*P* value	Standardized coefficient β	*P* value	Standardized coefficient β	*P* value	Standardized coefficient β	*P* value
Total EAT	−0.281	0.020*	−0.326	0.008*	−0.099	0.428	−0.280	0.026*
Age	−0.062	0.637	−0.029	0.826	0.246	0.074	−0.228	0.093
BMI	−0.182	0.160	−0.155	0.226	0.055	0.680	−0.150	0.256
Diabetes	0.263	0.034*	0.164	0.177	0.018	0.888	−0.112	0.371
HLP	−0.019	0.874	0.133	0.265	0.147	0.237	−0.117	0.341
Sex	−0.193	0.111	0.211	0.078	−0.285	0.024*	0.081	0.506
Ventricular EAT	−0.298	0.014*	−0.277	0.023*	−0.120	0.332	−0.254	0.042*
Age	−0.088	0.497	−0.064	0.626	0.229	0.084	−0.241	0.072
BMI	−0.188	0.145	−0.159	0.222	0.022	0.866	−0.136	0.307
Diabetes	0.267	0.030*	0.160	0.195	0.024	0.851	−0.111	0.379
HLP	−0.026	0.828	0.119	0.325	0.127	0.308	−0.125	0.313
Sex	−0.214	0.077	0.192	0.115	−0.299	0.019*	0.063	0.616
	LA LAS rest		LA LAS stress		RA LAS rest		RA LAS stress	
Atria	Standardized coefficient β	*P* value	Standardized coefficient β	*P* value	Standardized coefficient β	*P* value	Standardized coefficient β	*P* value
Total EAT	−0.284	0.018*	−0.274	0.039*	−0.425	<0.001*	−0.243	0.050
Age	−0.253	0.052	−0.319	0.015*	−0.146	0.263	−0.275	0.043*
BMI	−0.327	0.011*	−0.291	0.023*	−0.172	0.180	−0.122	0.350
Diabetes	0.186	0.122	0.022	0.851	−0.112	0.356	−0.116	0.350
HLP	0.021	0.855	−0.013	0.914	0.076	0.525	−0.115	0.348
Sex	−0.065	0.576	0.101	0.392	−0.037	0.753	0.130	0.288
Atrial EAT	−0.272	0.027*	−0.277	0.023*	−0.342	0.010*	−0.201	0.118
Age	−0.225	0.091	−0.283	0.033*	−0.106	0.437	−0.249	0.071
BMI	−0.313	0.015*	−0.279	0.028*	−0.119	0.367	−0.082	0.535
Diabetes	0.166	0.165	0.008	0.945	−0.149	0.240	−0.137	0.274
HLP	0.021	0.858	−0.008	0.948	0.077	0.538	−0.105	0.401
Sex	−0.030	0.799	0.137	0.247	0.017	0.890	0.167	0.186

BMI, body mass index; EAT, epicardial adipose tissue; HLP, hyperlipoproteinaemia; LA, left atrial; LAS, long axial strain; LV, left ventricular; RA, right atrial; RV, right ventricular.
Multivariable regression analysis of the association of atrial and ventricular long-axis strain with total, atrial, and ventricular EAT and patient characteristics in the overall cohort. Data are presented as the standardized association coefficient β with referring *P* values.
**P* values below 0.05 were considered statistically significant.

HFpEF,[15] provided further evidence for a potential interconnection of EAT volumes and diastolic dysfunction.

During the in-depth analysis of the underlying functional impairment, this study now precisely discriminated that patients with higher total EAT volume had impaired biventricular diastolic function during exercise stress only, while atrial strain was reduced at rest already. This could be explained by lower muscular strength of the atria with less capacities for the compensation of additional external pressure load induced by EAT. At the same time, atrial distensibility is diminished by the additive volume and pressure afterload of the left ventricle[7] and inflammatory reactions of the vulnerable atrial myocardium causing incremental damage and atrial functional impairment in advance to ventricular decompensation.[28,29]

This adds to the important role of the atrium in diastolic dysfunction.

Non-invasively quantified atrial function in diastolic dysfunction and HFpEF was confirmed as an important parameter in general for the diagnosis and prognostication in HFpEF as it is a key element in the disease's pathophysiology.[15,30,31] On the one hand, atrial EAT could aggravate commonly known haemodynamic challenges by further restriction and might limit the compensatory function of the atrium in ventricular diastole.[32]

On the other hand, those impairments by atrial EAT align with the assumption of the development of an atrial cardiomyopathy, which nurtures LA malfunction as a central role in diastolic dysfunction.[29,33]

As we now observe LV myocardial remodelling in the cohort with increased EAT volume, an early atrial decompensation in the disease progression associated with increased atrial EAT volume could help to identify patients before adverse remodelling occurs. However, the timely sequence of the development of EAT and fibrosis has yet to be investigated.

The distinct influences of increased EAT volumes and its regional parts yield important implications. The haemodynamic and functional alterations on ventricular and atrial function without morphological changes underline the need for an enhanced characterization and differentiation within the inhomogeneous and broad patient group suffering from diastolic dysfunction. Discriminating patients with increased

EAT volume and particularly increased atrial EAT volume could help to identify patients at risk for further functional deterioration. As sodium dependent glucose co-transporter 2 (SGLT-2) inhibitors were already observed to reduce EAT,[34,35] an improved phenotyping and the early identification of patients at risk could even guide those medical interventions to interfere in potentially reversible stages of heart failure.

Even though this has to be prospectively evaluated in future research, there could be a chance to modify the progression of early diastolic failure in patients with distinctive EAT patterns by simple lifestyle changes and early medical treatment.

Limitations

Patients included in this study were highly selected and might not represent the general population of patients with diastolic dysfunction. Furthermore, the trial was a monocentric study conducted in an experienced core lab, which limits its reproducibility in other centres.[14] The quantification of EAT volumes can be biased by partial volume effects, even though a highly standardized post-processing evaluation should reduce the probability for individual errors. The impact of EAT might be subject to further comorbidities or lifestyle factors, which have not been investigated in this study. Therefore, a direct association of EAT with diastolic dysfunction cannot be finally proven.

The small number of included patients potentially reduces the statistical accuracy and implies that at least some of the results could only be reported as a trend without statistical significance. Furthermore, this study mainly focuses on the associations between EAT and diastolic dysfunction. The pathophysiological interaction should be investigated in future prospectively randomized studies.

Conclusions

Increased EAT volumes in patients with dyspnoea and signs of diastolic dysfunction is associated with more severe cardiac diastolic failure and adverse remodelling and promotes the development of manifest HFpEF. Despite similar ventricular morphology, important differences in cardiac function were observed between patients with high and low EAT volumes. In patients with higher EAT volume, ventricular diastolic function could be compensated longer than atrial function, which was impaired at rest already. In this context, regional EAT seems to directly contribute to the deterioration of the associated chambers and points out to distinct phenotypes of patients with diastolic failure. Further investigations of those EAT phenotypes and their chronological appearance within heart failure development could enhance the understanding of the disease progression and help to identify potentially reversible stages for intervention before significant adverse remodelling occurs.

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Conflict of interest

None declared.

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