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ORIGINAL ARTICLE

Diverging role of epicardial adipose tissue across the entire heart failure spectrum

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Abstract

Aims Epicardial adipose tissue (EAT) is a metabolically highly active tissue modulating numerous pathophysiological processes. The aim of this study was to investigate the association between EAT thickness and endothelial function in patients with heart failure (HF) across the entire ejection fraction spectrum.

Methods and results A total of 258 patients with HF with an ejection fraction across the entire spectrum [HF with reduced ejection fraction (HFrEF), *n* = 168, age 60.6 ± 11.2 years; HF with preserved ejection fraction (HFpEF), *n* = 50, mean age 65.1 ± 11.9 years; HF with mildly reduced ejection fraction (HFmrEF), *n* = 32, mean age 65 ± 12] were included. EAT was measured with transthoracic echocardiography. Vascular function was assessed with flicker-light-induced vasodilation of retinal arterioles (FIDart%) and flow-mediated dilatation (FMD%) in conduit arteries. Patients with HFrEF have less EAT compared with patients with HFpEF (4.2 ± 2 vs. 5.3 ± 2 mm, respectively, $P < 0.001$). Interestingly, EAT was significantly associated with impaired microvascular function (FIDart%; $r = -0.213$, $P = 0.012$) and FMD% ($r = -0.186$, $P = 0.022$), even after multivariate correction for confounding factors (age, body mass index, hypertension, and diabetes; standardized regression coefficient (SRC) = −0.184, $P = 0.049$ for FIDart% and SRC = −0.178, $P = 0.043$ for FMD%) in HFrEF but not in HFpEF.

Conclusions Although less EAT is present in HFrEF than in HFpEF, only in HFrEF EAT is associated with vascular dysfunction. The diverging role of EAT in HF and its switch to a functionally deleterious tissue promoting HF progression provide the rationale to specifically target EAT, in particular in patients with reduced ejection fraction.

Keywords Heart failure; Epicardial adipose tissue; Endothelial function; Flow-mediated dilatation; Retinal vascular function

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Introduction

Epicardial adipose tissue (EAT) is a paracrine organ constituted by a layer of adipose tissue directly located between the myocardium and the visceral pericardium.[1] The epicardial fat layer originates from mesothelial cells, sharing the same microcirculation as the myocardium.[2] In physiological conditions, EAT exerts protective effects typical of brown-like fat tissue: It burns excess fatty acids, which otherwise may interfere with the electromechanical cardiac coupling, produces cytokines nourishing the heart, secretes adiponectin limiting hypertrophic stimuli, and finally reduces inflammation and fibrosis, both in the myocardium and in the coronary arteries.[3] Furthermore, under ischaemic conditions, it might serve as a ready source of free fatty acids to promptly provide myocardial energy.[4]

On the other hand, there is increasing evidence that EAT in certain conditions—such as in obesity—might switch to properties comparable with white adipose tissue, thereby promoting lipolysis and producing proinflammatory adipokines and activating profibrotic pathways.[5] As such, increased EAT thickness has been attributed with a metabolic phenotype (obesity, insulin resistance, dyslipidaemia, and hypertension), overt and subclinical coronary artery disease, and adverse cardiovascular events.[6] Importantly, EAT may be an easily quantifiable marker of visceral adiposity, which is related to metabolic syndrome and cardiovascular risk factors.[2]

Growing evidence suggests that increased EAT thickness has detrimental effects in patients with heart failure (HF) with preserved ejection fraction (HFpEF), where it is associated with increased inflammatory cytokines and higher ventricular filling pressures.[7–9] On the other hand, EAT thickness was shown to be reduced in HF with reduced ejection fraction (HFrEF).[1,10,11] The role of EAT across the entire spectrum of ejection fraction is currently poorly understood. Given the importance of vascular function in HF[12,13] and its association with the development, progression, and prognosis of the disease, the association between the metabolically active EAT and the vasculature is of particular interest.

Thus, the aim of this study was to investigate whether there is an association between EAT thickness and vascular function, assessed by both retinal vessel analysis (RVA) and flow-mediated dilatation (FMD), respectively.

Methods

Study design and protocol

In this retrospective observational analysis, 258 patients with chronic HF prospectively included into our RVA-cohort study between January 2015 and December 2021 were used. The study protocol was approved by the local ethics committee of canton Zurich (KEK-ZH-2014-0329). HF and classification into HFrEF, HF with mildly reduced ejection fraction (HFmrEF), and HFpEF were performed according to the current guidelines.[14]

Exclusion criteria were photosensitive epilepsy, glaucoma or other relevant eye pathology, allergy to study drugs, current acute illness, pregnancy, or breastfeeding.

The evaluation of vascular function was performed in the morning. Patients were instructed to fasten for at least 8 h (except water), to avoid coffee and alcohol consumption for at least 12 h, and not to perform intense physical activity the days prior to examination. Regular medications were allowed to be taken before examination, with the exception of antidiabetic medications. Medical history, assessment of clinical parameters, laboratory blood tests, and evaluation of vascular function (starting with vascular stiffness assessment, followed by RVA and, finally, FMD) were performed. All participants signed a written informed consent prior to inclusion. Permission to collect further clinical data, including EAT measurements, was obtained by signing a general consent agreement.

Echocardiography and assessment of epicardial adipose tissue

Transthoracic echocardiography was obtained during regular clinical outpatient visits using 2D, M-mode, and colour Doppler echocardiography by experienced cardiologists. All examinations were performed in a time frame of ±12 months within vascular function measurements. EAT was measured retrospectively by a single expert cardiologist (V. A. R.) and, in case of doubt, the opinion of an expert and blinded cardiologist was sought.

EAT thickness was measured as the echo-free space between the outer wall of the right ventricle and the visceral pericardium in the parasternal long-axis view at end-systole, perpendicularly to the aortic annulus. This point presents the highest absolute EAT thickness and represents a simple, cost-effective, and practical measure in daily clinical practice and in research settings.[4] Another measurement was performed between the outer wall of the right ventricle and the visceral pericardium in the parasternal short-axis view at end-systole, perpendicularly to the papillary muscles. The average values from two cardiac cycles of both locations were calculated.[6] Both the HFrEF and HFpEF groups were divided according to their EAT median values.

Assessment of microvascular endothelial function: retinal vessel analysis

Static and dynamic RVA as a marker of microvascular endothelial function was conducted using an Imedos Dynamic Retinal Vessel Analyzer (Imedos, Jena, Germany). Dynamic vessel analysis measures dilatation of retinal vessels after provocation with flicker light, according to our established protocols.[12] FIDart% and FIDven%, that is, respectively the arteriolar and venular vasodilatation in response to flickering light, were analysed and expressed as percentage variation compared with baseline. To calculate these parameters, the maximal vascular response during the last 10 s of each flickering-light episode or during the 3 s following it was identified.[15] This maximal value was averaged with the 2 s before and after it. Episodes with $<$50% of valid measurements during this period were excluded from calculation. Furthermore, the areas under the FIDart and FIDven curves were calculated.

Static vessel analysis was performed by obtaining monochromatic fundus photographs using the static CCD camera and VesselMap 2 software according to our established protocol.[12] The central retinal arteriolar equivalent (CRAE) and the central retinal venular equivalent (CRVE) were automatically calculated. Both values are used to calculate the arteriolar–venular retinal ratio (AVR) (AVR = CRAE/CRVE).

Assessment of endothelial function in conduit arteries: flow-mediated dilatation

FMD was measured in supine position according to established protocols. Briefly, a 10 MHz linear array transducer

(Siemens Acuson X300 and Juniper, Siemens AG) was used to assess the arterial diameter of one brachial artery in baseline condition for 1 min. A blood pressure cuff was placed distally and inflated 50 mmHg above systolic pressure for 5 min. After release, the brachial artery diameter was measured for further 4 min. An automatic wall-tracking and analysis software (FMD-Studio, Pisa, Italy) provided continuous wall-to-wall measurements. The percentage peak dilatation during the hyperaemic phase in relation to the baseline resting diameter was calculated (FMD%). To evaluate for endothelial-independent effects, the percentage peak dilation of the brachial artery 6 min after one dose of sublingual glycerol trinitrate (GTN nitrolingual 0.4 mg) was performed. The reproducibility of our laboratory's measurements has already been published.[16]

Arterial stiffness

A SphygmoCor applanation tonometer system (AtCor Medical, Itasca, IL, USA) was used to measure heart rate-corrected augmentation index (AIx@75) and pulse wave velocity (PWV) according to established protocols.[17]

Laboratory assessment

Blood samples were drawn in fasted state and analysed on the same day at the Institute of Clinical Chemistry at the University Hospital of Zurich using standard methods. High-sensitivity troponin-T and N-terminal prohormone of brain natriuretic peptide (NT-proBNP) were quantified using electrochemiluminescence immunoassays and the COBAS8000 autoanalyser of Roche Diagnostics (Mannheim, Germany). Undetectable values were replaced by half the lower limit of detection.

Statistical analysis

Statistical analyses and computations were performed using the SPSS software (v25, SPSS Inc., USA) and Python (v3.9.7, Python Software Foundation, Oregon, USA). Continuous variables are presented as mean (± standard deviation) for normal distribution and median (± interquartile range) for skewed distribution. Categorical variables are expressed as percentage, unless otherwise stated. Differences in baseline characteristics between the groups were assessed by independent Student's *t*-test or ANOVA for parameters with parametric distribution, while Mann–Whitney *U* test or Kruskal–Wallis tests were used for parameters with a non-normal distribution. Pearson's χ^2 test or Fisher's exact test was calculated for dichotomic variables.

Univariable analysis for relevant clinical covariates was performed using Pearson's or Spearman's test, as appropriate. Multivariable regression analyses were performed with a stepwise approach, and the strength of relationships was tested with *F*-test ANOVA. Standardized regression coefficients (SRCs) are reported for single parameters. Independent variables were tested for interaction via multicollinearity statistics, and only models having a variance inflation factor < 1.5 for each parameter were selected.

Survival analyses were performed by Kaplan–Meier curves, and a log-rank test was performed to test for significant differences between patients with higher EAT thickness ≥ 3.9 mm compared with those with an EAT thickness < 3.9 mm. Cox's regression analyses with correction for confounding factors (age, gender, and presence of ischaemic disease) were performed to investigate the hazard ratio (HR) of increased EAT (presented as categorical variable with the cut-off of 3.9 mm) and FIDart%. Investigated outcomes (major cardiovascular events defined as myocardial infarction, hospitalization due to HF, stroke, and coronary revascularization), cardiovascular death, and all-cause death were extracted from the clinical database. A two-sided *P*-value of <0.05 was considered to be statistically significant.

Results

Study population

Baseline characteristics of patients with HFrEF (n = 168, 65%), HFmrEF (n = 32, 12%), and HFpEF (n = 50, 19%) are shown in *Table 1A*. Patients with HFrEF were significantly younger and were more likely to be male compared with patients with HFpEF. NT-proBNP values were similarly elevated across the entire spectrum of HF. Patients with HFmrEF had EAT thickness values comparable with patients with HFpEF (*Table 1A*).

Epicardial adipose tissue across the heart failure spectrum

Patients with HFrEF presented with less EAT as compared with patients with HFpEF (4.2 ± 2 vs. 5.3 ± 2 mm, $P < 0.001$; *Table 1A*). For better readability, we divided HFrEF and HFpEF patients into two groups according to their EAT median values (*Tables 1B* and *2*). Patients with HFrEF and more EAT (>3.9 mm) had significantly higher body mass index (BMI) (despite similar amount of pericardial fat) and were more likely to be male. They have more comorbidities such as hypertension, diabetes, and coronary artery disease and were more likely to be treated with calcium antagonists, statins, and metformin (*Table 1B*).

Table 1A Baseline characteristics of the study participants

Variable	All patients $N = 258$	HFrEF $N = 168$	HFmrEF $N = 32$	HFpEF $N = 50$	*P*-value of HFrEF vs. HFpEF
Age, years	61.8 (11.7)	60.6 (11.2)$^{\#,\ddagger}$	65 (12)*	65.1 (11.9)	0.015
BMI, kg/m^2	27.5 (5.1)	27.6 (5.2)	28.4 (6)	26.9 (4.5)	0.393
Female gender	56 (22)	26 (15)‡	7 (22)	21 (42)	<0.001
Echocardiography					
EAT, cm	0.48 (0.2)	0.42 (0.2)$^{\#,\ddagger}$	0.58 (0.3)*	0.53 (0.2)*	<0.001
LVEF, %	35.9 (14.4)	27.1 (8)$^{\#,\ddagger}$	44.1 (4.9)*,‡	56.9 (4.4)*,$^{\#}$	<0.001
LVEF, % at diagnosis	39.5 (16.4) $n = 97$	31.6 (12.1)$^{\#,\ddagger}$ $n = 52$	41.1 (14.6)* $n = 19$	61.4 (6.2)* $n = 18$	<0.001
LVEDVI, mL/m^2	83.4 (36.8)	100.5 (35.1)$^{\#,\ddagger}$	60.5 (17.9)*,‡	49 (11.4)*,$^{\#}$	<0.001
LAVI, mL/m^2	42.9 (14.2)	43.3 (14.6)	40.1 (13.9)	45.5 (13.4)	0.376
E/e′	14.3 (8.3) $n = 171$	14.1 (8.3) $n = 103$	12.8 (6.3) $n = 24$	17.4 (9.9) $n = 34$	0.059
RV fac, %	36.2 (8.2)	35.1 (8.7)	37.6 (7.4)	38 (7.1)	0.052
Therapy					
RAAS antagonists	191 (74)	142 (86)‡	26 (81)‡	14 (28)$^{\#}$	<0.001
Beta-blockers	189 (74)	140 (83)‡	25 (78)‡	22 (44)$^{\#}$	<0.001
Loop diuretics	179 (71)	124 (74)	23 (72)	35 (70)	0.867
MRA	119 (47)	104 (62)$^{\#,\ddagger}$	8 (25)*	7 (14)	<0.001
Statins	162 (64)	118 (70)‡	19 (59)	20 (40)	0.001
Metformin	31 (12)	24 (14)	4 (13)	3 (6)	0.251
Insulin	21 (8)	16 (10)	3 (9)	2 (4)	0.415
Clinical conditions					
AF	59 (32)	31 (33)	7 (23)	18 (36)	0.824
Hypertension	139 (53)	92 (55)	15 (47)	25 (50)	0.666
Dyslipidaemia	132 (51)	97 (42)$^{\#,\ddagger}$	11 (66)*	20 (60)	0.041
Diabetes	79 (31)	62 (37)‡	6 (19)	9 (18)	0.017
MI	48 (19)	44 (26)$^{\#,\ddagger}$	2 (6)*	2 (4)	0.001
CAD	133 (52)	112 (33)$^{\#,\ddagger}$	9 (72)*	9 (18)	<0.001
Blood tests					
Hb, g/L	133.3 (19.5)	133.2 (19.9)	136.6 (13.9)	130.6 (21.5)	0.456
Leucocytes, G/L	6.8 (1.9)	7 (1.9)‡	6.5 (1.5)	6.2 (2)	0.012
eGFR, mL/min	62.8 (22.6)	64.2 (21.3)‡	64.3 (23.1)	54.5 (26.2)	0.010
hs-CRP, mg/L	2.2 (1.1–6.4)	2.4 (1–7.1)	2.1 (1.1–4.8)	2.1 (1.1–4.3)	0.218
hs-TnT, ng/L	17 (10–34)	18 (10–33)	13 (9–20)‡	29 (16–60)$^{\#}$	0.069
NT-proBNP, ng/L	906 (316–1967)	974 (378–2154)	709 (140–1598)	978 (432–2158)	0.400
Glucose, mmol/L	6.5 (2.2)	6.8 (2.5)	5.8 (1)	6 (1.6)	0.054
LDL-c, mmol/L	2.3 (1)	2.2 (0.9)‡	2.6 (1.1)	2.8 (1.3)	0.002

AF, atrial fibrillation; BMI, body mass index; CAD, coronary artery disease; EAT, epicardial adipose tissue; eGFR, estimated glomerular filtration rate; Hb, haemoglobin; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; hs-CRP, high-sensitivity C-reactive protein; hs-TnT, high-sensitivity troponin-T; LAVI, left atrial volume indexed for body surface area (BSA); LDL-c, low-density lipoprotein cholesterol; LVEDVI, left ventricular end-diastolic volume indexed for BSA; LVEF, left ventricular ejection fraction; MI, myocardial infarction; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; RAAS, renin-angiotensin-aldosterone system; RV fac, right ventricular fractional area change.

Values are mean ± standard deviation, *n* (%), or median [25th quartile, 75th quartile]. Complete blood tests were available in 24 patients in the HFmrEF group and in 38 patients in the HFpEF group. Echocardiography was available for 155 patients in the HFrEF group, 31 patients in the HFmrEF group, 8 patients in the heart failure with improved ejection fraction group, and 42 patients in the HFpEF group.

*$P < 0.05$ vs. HFrEF.

#$P < 0.05$ vs. HFmrEF.

‡$P < 0.05$ vs. HFpEF.

Similarly, patients with HFpEF and a thicker EAT (>5.5 mm) had significantly higher BMI (despite no differences in pericardial fat) and had more hypertension. No differences were found with respect to other comorbidities or therapy (*Table 1B*).

HFrEF patients with underlying non-ischaemic disease have less EAT as compared with HFrEF patients with coronary artery disease (3.8 ± 1 vs. 4.4 ± 2 mm, $P = 0.027$; Supporting Information, *Table S1*).

Vascular function

Microvascular function (flicker-light induced arterial dilatation; FIDart%)

In HFrEF, microvascular function was significantly worse in patients with a higher amount of EAT (>3.9 mm) as compared with those with less EAT [0.9% (0.3–2.2) vs. 1.6% (0.8–2.5), $P = 0.018$] (*Table 2* and *Figure 1*). On the contrary, in HFpEF, FIDart% was better in patients with a higher

Table 1B Baseline characteristics of the study participants

Variable	HFrEF			HFpEF		
	EAT ≤ 3.9 mm *N* = 78	EAT > 3.9 mm *N* = 71	*P*-value	EAT ≤ 5.5 mm *N* = 24	EAT > 5.5 mm *N* = 18	*P*-value
Age, years	59.6 (12.4)	61.8 (9.3)	0.215	64.5 (11.6)	64.2 (13.8)	0.933
BMI, kg/m^2	26.8 (4.6)	28.8 (5.4)	0.015	25.3 (3.6)	29.5 (4.5)	0.002
Female gender, %	22 (20)	8 (6)	0.014	15 (63)	7 (39)	0.212
Therapy and comorbidities						
RAAS inhibitors, %	85 (76)	88 (64)	0.674	6 (25)	6 (38)	0.626
Beta-blockers, %	65 (83)	65 (92)	0.395	7 (29)	10 (63)	0.113
Loop diuretics, %	59 (74)	57 (80)	0.593	19 (79)	11 (69)	0.318
MRA, %	49 (62)	50 (68)	0.517	4 (17)	3 (19)	0.810
Ca antagonists, %	8 (7)	21 (15)	0.021	2 (8)	5 (31)	0.165
Statins, %	63 (55)	84 (61)	0.003	9 (38)	9 (56)	0.482
Metformin, %	9 (8)	21 (15)	0.039	0	3 (19)	0.080
Insulin, %	8 (7)	12 (9)	0.356	0	2 (13)	0.181
Atrial fibrillation, %	15 (54) (*n* = 44)	13 (33) (*n* = 40)	1	7 (29)	8 (44)	0.347
Hypertension, %	48 (43)	65 (48)	0.028	8 (33)	13 (72)	0.028
Dyslipidaemia, %	53 (48)	65 (48)	0.136	9 (38)	10 (56)	0.349
Diabetes, %	23 (20)	55 (41)	<0.001	2 (8)	6 (33)	0.041
MI, %	25 (22)	30 (22)	0.473	1 (4)	1 (6)	1
CAD, %	61 (54)	80 (58)	0.010	4 (17)	4 (25)	0.694
Laboratory						
Leucocytes, G/L	7.1 (2.1)	6.9 (1.9)	0.660	5.9 (2.4)	6.6 (1.7)	0.305
eGFR, mL/min	68.5 [48–86]	62.5 [47–76]	0.154	50 [33–71]	60 [42–74]	0.432
hs-CRP, mg/L	2.4 [1.1–7.8]	2.7 [1–6.6]	0.924	1.9 [1.3–7.8]	2.2 [1.6–5.6]	0.788
hs-TnT, ng/L	16 [10–31]	21 [11–35]	0.262	33.5 [14–107]	23.5 [12–37]	0.180
NT-proBNP, ng/L	974 [394–3002]	893 [296–1687]	0.151	1011 [563–4312]	922 [304–1333]	0.073
Glucose, mmol/L	6.6 (2.6)	7.3 (2.4)	0.156	5.7 (1.2)	7 (2)	0.041
LDL-c, mmol/L	1.2 (0.3)	2.1 (0.8)	0.119	3.1 (1.5)	2.5 (1)	0.195
Echocardiography						
LVEF, %	26.3 (8.2)	27.3 (7.8)	0.447	56.3 (4.6)	57.5 (3.7)	0.382
LVEDVI, mL/m^2	106 (35)	96 (36)	0.103	48.2 (11)	50.6 (12.1)	0.505
LAVI, mL/m^2	44.4 (14.5)	42.2 (15.2)	0.404	48.4 (15.3)	40.5 (9.6)	0.041
E/e'	13.2 (8.1)	14.7 (8.5)	0.364	16.6 (9.3)	18.4 (11.3)	0.619
TAM, mm	15.1 (4.4)	15.4 (4.3)	0.687	16 (5.2)	17.3 (4.7)	0.435
RV fac, %	34.9 (8.8)	35.6 (8.8)	0.637	37.1 (7.7)	39.5 (6.2)	0.282
Pericardial fat, mm	6 (3)	1.7 (8.4)	0.252	6.7 (2.1)	6.6 (2.6)	0.905

BMI, body mass index; CAD, coronary artery disease; E, early diastolic mitral inflow velocity; e', early diastolic mitral annulus velocity; EAT, epicardial adipose tissue; eGFR, estimated glomerular filtration rate; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; hs-CRP, high-sensitivity C-reactive protein; hs-TnT, high-sensitivity troponin-T; LAVI, left atrial volume indexed for body surface area (BSA); LDL-c, low-density lipoprotein cholesterol; LVEDVI, left ventricular end-diastolic volume indexed for BSA; LVEF, left ventricular ejection fraction; MI, myocardial infarction; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; RAAS, renin-angiotensin-aldosterone system; RV fac, right ventricular fractional area change; TAM, tricuspid annular motion.
Values are mean ± standard deviation, *n* (%), or median [interquartile range].

amount of EAT (>5.5 mm) compared with patients with a smaller amount [3.5% (1.5–7.4) vs. 1.7% (1.2–3.7), *P* = 0.036] (*Table 2* and *Figure 2*).

After correcting for potential confounder (age, hypertension, diabetes, and BMI) in a multivariate regression analysis, EAT thickness remained the only independent predictor of impaired FIDart% in HFrEF but not in HFpEF (SRC = −0.184, *P* = 0.049) (*Table 3*).

Flicker-light-induced *venular* dilatation was significantly higher in those with thicker EAT. No differences were found in the baseline arteriolar or venular equivalent diameters (CRAE and CRVE), nor in their ratio (AVR).

Endothelial function in conduit arteries

EAT was significantly associated with impaired endothelial function in conduit arteries (FMD%; *r* = −0.186, *P* = 0.022). In HFrEF, FMD was significantly worse in patients with a higher amount of EAT (>3.9 mm) as compared with those with less EAT (5.7 ± 3.4 vs. 6.7 ± 3.8, *P* = 0.083). In HFpEF, FMD was not related to the amount of EAT. After correction for the same confounder as above, EAT thickness remains the only predictor for impaired FIDart% in HFrEF (FMD% as dependent variable: SRC = −0.165, *P* = 0.024) (*Table 3*).

Cardiometabolic profile

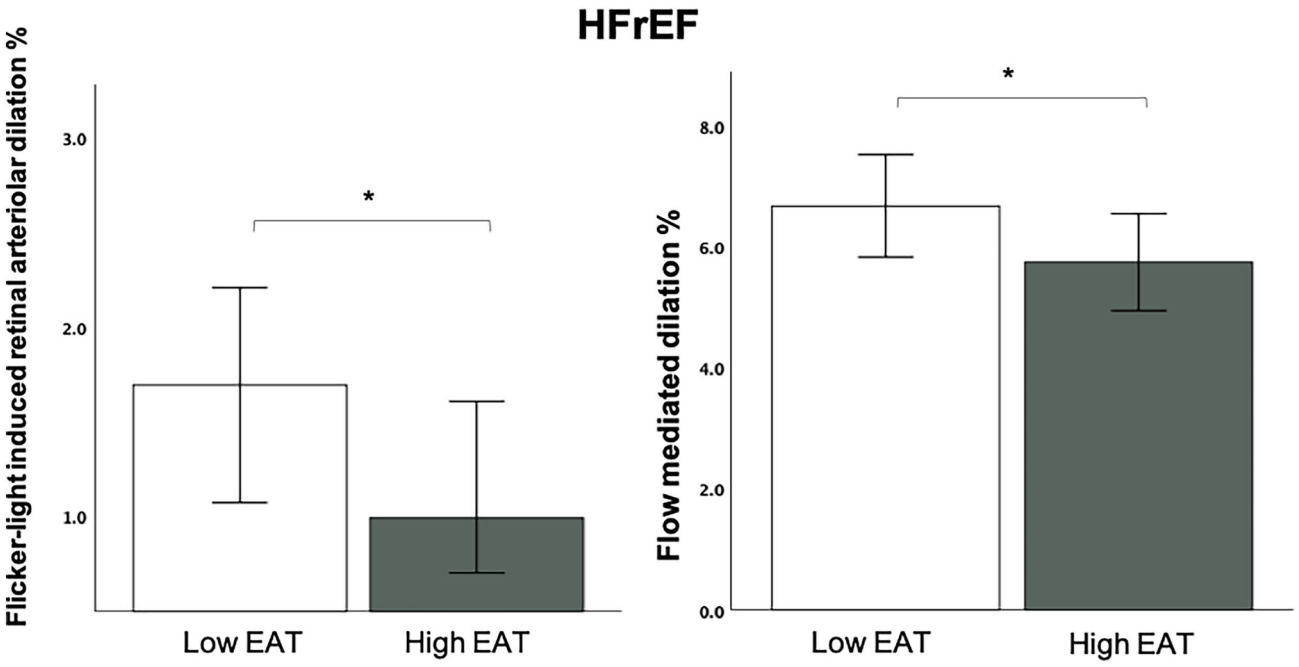
In the overall HF population, higher EAT was associated to higher BMI (*r* = 0.328, *P* < 0.001), hypertension (*r* = 0.180, *P* = 0.005), and diabetes mellitus (*r* = 0.211, *P* = 0.001). In our population, only age and BMI were independently related

Table 2 Vascular parameters

Variable	HFrEF			HFpEF		
	EAT ≤ 3.9 mm *N* = 78	EAT > 3.9 mm *N* = 71	*P*-value	EAT ≤ 5.5 mm *N* = 16	EAT > 5.5 mm *N* = 20	*P*-value
FIDart, %	1.6 [0.8–2.5]	0.9 [0.3–2.2]	0.018	1.7 [1.2–3.7]	3.5 [1.5–7.4]	0.036
FIDven, %	2.8 [1.9–4.3]	3.8 [2.8–4.8]	0.015	4.1 [2.3–5.3]	3.8 [3.4–4.9]	0.775
Area FIDart, mu * s	20 [2.3–36]	6.5 [0–33]	0.036	23 [1–53]	29 [5–88]	0.363
Area FIDven, mu * s	54 [22–89]	66 [35–94]	0.105	64 [38–114]	68 [46–88]	0.447
AVR	0.9 (0.1)	0.9 (0.1)	0.821	0.9 (0.1)	0.9 (0.1)	0.586
CRAE	196 (17.2)	192 (14.6)	0.121	185 (20.2)	178 (17.4)	0.297
CRVE	224 (27)	219 (26.1)	0.283	214 (22.6)	208.9 (11.9)	0.441
FMD, %	6.7 (3.8)	5.7 (3.4)	0.083	4.8 (2.4)	6 (3.9)	0.319
GTN, %	18.7 (7.3)	17.4 (6.2)	0.293	17 (7.3)	12.6 (4)	0.111
PWV, m/s	7.8 (2.4)	8.9 (2.7)	0.033	9.3 (2.6)	9.2 (3.6)	0.279

Area FIDart, total flickering-light-induced arteriolar vasodilation over time; Area FIDven, total flickering-light-induced venular vasodilation over time; AVR, arteriolar–venular retinal ratio; CRAE, central retinal arteriolar equivalent; CRVE, central retinal venular equivalent; EAT, epicardial adipose tissue; FIDart, flickering-light-induced arteriolar vasodilation; FIDven, flickering-light-induced venular vasodilation; FMD, flow-mediated dilatation; GTN, nitroglycerin-mediated vasodilation; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; mu, measuring units; PWV, pulse wave velocity.
Values are mean ± standard deviation, *n* (%), or median [interquartile range].

Figure 1 Difference in flicker-light-induced retinal arteriolar dilation in patients with heart failure with reduced ejection fraction (HFrEF) and reduced epicardial adipose tissue (EAT) thickness ≤ 3.9 mm vs. patients with HFrEF and increased EAT thickness > 3.9 mm. **P*-value < 0.05.



to EAT after correction for confounding factors (SRC = 0.14, $P = 0.044$ and SRC = 0.312, $P < 0.001$, respectively).

There was an inverse correlation between EAT and NT-proBNP ($r = -0.194$, $P = 0.003$), while there was no correlation with parameters of systemic inflammation (high-sensitivity C-reactive protein and leucocytes) or myocardial damage (high-sensitivity troponin-T).

Follow-up

Clinical outcome from clinical database (mean follow-up: 39.1 ± 21.4 months) was available for 221 subjects in the overall HF population. The most common adverse events were decompensated HF (*n* = 39, 18%) and cardiovascular death (*n* = 29, 13%).

Figure 2 Difference in flicker-light-induced retinal arteriolar dilation in patients with heart failure with preserved ejection fraction (HFpEF) and reduced epicardial adipose tissue (EAT) thickness ≤ 5.5 mm vs. patients with HFpEF and increased EAT thickness > 5.5 mm. ns, not significant.

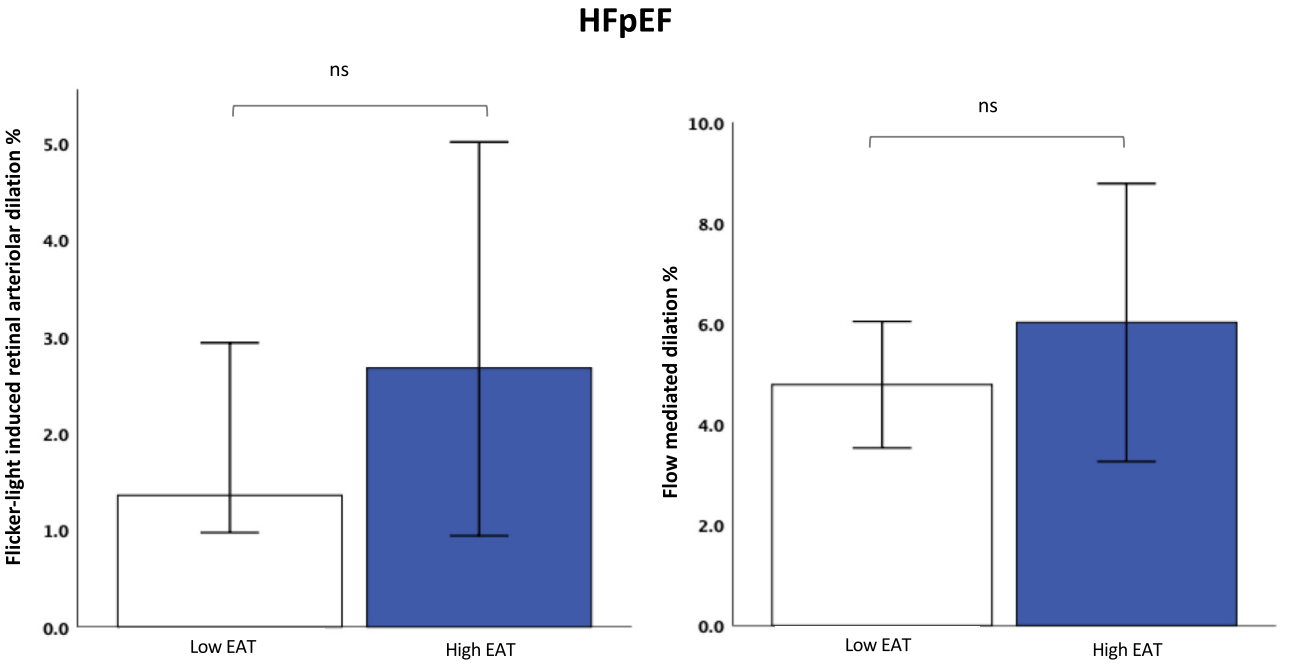


Table 3 Multivariable regression analysis to determine the contribution of epicardial adipose tissue (EAT) on vascular function (FMD%, PWV, and FIDart) in the overall heart failure population

	All HF						HFrEF				HFpEF	
	FMD		PWV		FIDart		FMD		FIDart		FIDart	
	N = 207		*N* = 175		*N* = 214		*N* = 164		*N* = 134		*N* = 36	
Model 1	**SRC**	***P***	**SRC**	***P***	**SRC**	***P***	**SRC**	***P***	**SRC**	***P***	**SRC**	***P***
EAT	−0.165	0.024	0.185	0.014	0.077	0.309	−0.178	0.043	−0.184	0.049	0.276	0.188
Age	−0.186	0.010	0.323	<0.001	−0.064	0.379	−0.149	0.085	0.014	0.119	−0.207	0.237
BMI	0.063	0.404	−0.004	0.958	0.022	0.774	0.062	0.480	−0.026	0.782	0.116	0.556
Arterial hypertension	−0.120	0.091	0.126	0.081	0.030	0.685	−0.166	0.050	−0.031	0.740	−0.058	0.767
Diabetes mellitus	0.043	0.545	0.038	0.599	−0.070	0.336	0.053	0.553	−0.029	0.767	0.099	0.593
P	0.002		<0.001		0.698		0.011		0.001		0.245	
Adj. R^2	0.069		0.214		−0.009		0.066		0.148		0.057	
Model 2	***N* = 121**		***N* = 108**		***N* = 148**		***N* = 107**		***N* = 125**		***N* = 22**	
EAT	−0.169	0.068	0.149	0.125	0.219	0.016	−0.202	0.040	0.247	0.011	0.107	0.736
Atrial fibrillation	0.183	0.058	0.063	0.521	0.045	0.595	0.202	0.046	0.027	0.761	0.061	0.838
LAVI	−0.171	0.076					−0.234	0.022				
Age	−0.210	0.025	0.269	0.008	−0.084	0.346	−0.220	0.023	−0.164	0.082	0.088	0.777
Arterial hypertension	−0.029	0.746	0.130	0.169	−0.080	0.361	0.026	0.783	−0.095	0.303	−0.145	0.644
BMI			0.054	0.414	−0.075	0.421			−0.073	0.458	−0.020	0.954
P	0.039		0.002		0.209		0.015		0.070		−0.254	
Adj. R^2	0.056		0.125		0.015		0.085		0.042		0.989	

BMI, body mass index; EAT, epicardial adipose tissue; FIDart, flickering-light-induced arteriolar vasodilation; FMD, flow-mediated dilatation; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; LAVI, left atrial volume indexed for body surface area; PWV, pulse wave velocity; SRC, standardized regression coefficient.
To reduce overfitting issues, in the subgroup analyses, only those parameters that were significant in the correlations were analysed.

Patients with HFrEF and increased EAT thickness ≥ 3.9 mm did not have more major advanced cardiovascular events (MACE; myocardial infarction, hospitalization due to HF, coronary revascularization, and stroke) as compared with those with low EAT < 3.9 mm [*n* = 71, 43%, HR 0.76 m, 95% confidence interval (CI) 0.47–1.23, *P* = 0.407]. Myocardial infarction occurred in 2 subjects (1.4%), hospitalization due to decompensated HF in 29 patients (20%, HR 0.78, 95% CI

0.37–1.63, $P = 0.819$), death due to cardiovascular reasons in 22 patients (15%, HR 0.78, 95% CI 0.33–1.86, $P = 0.546$), and death due to all causes in 12 patients (8.3%, HR 1.23, 95% CI 0.39–4.1, $P = 0.520$). No increased adverse events were found with respect to FIDart after correction for age, gender, and presence of ischaemic heart disease (cardiovascular death: HR 0.9, 95% CI 0.62–1.26; all-cause mortality: HR 0.8, 95% CI 0.51–1.25; MACE: HR 0.95, 95% CI 0.76–1.2).

In both models, elevated age was the only adverse prognostic factor for cardiovascular death (HR 1.09, 95% CI 1.03–1.14, $P = 0.001$ for the model investigating EAT prognostic value and HR 1.08, 95% CI 1.02–1.14, $P = 0.008$ for the model investigating FIDart prognostic value).

Discussion

In this study, we confirm previous findings of less EAT in HFrEF than in HFpEF patients. While in HFpEF no clear association between EAT and endothelial function was seen, patients with HFrEF showed a strong, independent, and significant association of EAT with vascular dysfunction, in larger conduit arteries and in the microcirculation alike. However, the design of the current study does not permit to draw conclusions on a direct mechanistic link of EAT with vascular function. Given the importance of endothelial dysfunction in HF, the association of EAT and the vasculature should be further evaluated.

Heart failure and endothelial function

Endothelial dysfunction represents one of the initial steps in the development of atherosclerosis. There are several possibilities to quantify endothelial function. RVA is an easy to access, standardized, and non-invasive window to investigate the microcirculation at the back of the eye.[16,18] Retinal vascular vasodilatory response to flicker-light stimulation is mainly related to neurovascular coupling promoting endothelial nitric oxide (NO) release and, therefore, represents an important marker for microvascular endothelial dysfunction.[19] Reduced FIDart% is associated with traditional cardiovascular risk factors such as hypertension, dyslipidaemia, diabetes mellitus, obesity, and chronic kidney disease and may even better predict long-term adverse cardiovascular events as compared with traditional cardiovascular risk factors.[20] In a previous study, we demonstrated that FIDart% is impaired in a *continuum* over the whole spectrum of ischaemic heart disease with lowest values in patients with overt HF due to ischaemic heart disease.[12,13]

The reason for impaired microvascular function in HF patients is not completely understood. In this study, we assessed whether the reported decrease in FIDart% may, at least in part, be associated with EAT.

Epicardial adipose tissue and heart failure

EAT is an endocrine and paracrine active tissue in direct continuity with the myocardium, which, in pathological conditions, acquires a proatherogenic transcriptional profile resulting in increased synthesis of biologically active adipokines with proinflammatory properties.[2,21]

Although there is increasing evidence of the role of increased EAT thickness in patients with HFpEF and obesity, the role of EAT in patients with HFrEF is not clear and controversial. Indeed, up to now, EAT has been mainly considered as an energy source by secreting nurturing adipokines, and the lower values observed in HFrEF as compared with healthy subjects and to patients with HFpEF have been seen as adverse sign of cardiac cachexia, whereas higher values have been associated with a better outcome.[22,23] In this study, we report on a median EAT thickness of 3.9 mm in HFrEF and 5.5 mm in HFpEF, which is similar to current literature for HF patients.[22] Interestingly, we observed more EAT in HFrEF patients with ischaemic heart disease as compared with patients with HFrEF due to other aetiologies (most commonly dilated cardiomyopathy).

Our findings are supported by previous studies, where higher EAT thickness has been observed in patients with coronary artery disease as compared with those without, and EAT was demonstrated to be proatherogenic and related to increased inflammation and oxidative stress.[2] Indeed, EAT harvested during elective coronary artery bypass graft surgery was found to express high levels of proinflammatory cytokines irrespective of clinical characteristics and plasma concentrations of circulating biomarkers.[24] Furthermore, in patients with ischaemic cardiovascular disease, EAT presents with a proatherogenic transcriptional profile independent from the level of inflammation in other fat depots, thus supporting the hypothesis of a local, paracrine, effect of EAT.[24,25]

In the present study, we did not find differences in inflammatory parameters based on EAT thickness, for example, leucocytes count and high-sensitivity C-reactive protein. It is of note that HFrEF patients with increased EAT thickness were more frequently under statin therapy, which has pleiotropic anti-inflammatory effects. However, as previously reported, current therapies (such as chronic use of statins or angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers) do not appear to reduce local inflammatory signalling in EAT.[24]

Epicardial adipose tissue and retinal arteriolar function

In this study, we found a stronger impairment of vascular function in HF patients with more EAT as compared with those with less EAT. Interestingly, our data suggest diverging roles of EAT in HFrEF as compared with HFpEF patients.

The mechanistic association between deranged EAT properties and endothelial dysfunction is not well understood, yet. Recently, we demonstrated impaired retinal microvascular function as assessed by FIDart% in patients with overt coronary artery disease as compared with those without.[12,13]

Although patients with increased EAT thickness were more likely to be diabetic and treated with antidiabetic therapy, insulin therapy and metformin use were not different and both groups showed similar glucose control. Furthermore, no differences were found for high-sensitivity troponin-T and NT-proBNP, although HFrEF patients with an increased EAT thickness were more likely to have hypertension and coronary artery disease. To correct for these possible confounders, we performed a multivariable analysis with adjustment for clinically relevant confounding factors (diabetes, age, hypertension, BMI, and atrial fibrillation). Importantly, we showed that EAT remained an independent predictor of impaired endothelial function both in conduit arteries and in the microcirculation in HFrEF patients.

On the contrary, no association was found between increased EAT thickness and endothelial function in HFpEF patients.

As such, we postulate that increased EAT may exert a negative effect on systemic endothelial function and that its pathophysiology is likely different in HFrEF as in HFpEF.

Of note, HFpEF is a syndrome with heterogeneous aetiologies, so that it may be difficult to find a common denominator.

Epicardial adipose tissue and retinal venular function

Although patients with a higher amount of EAT do have impaired microvascular function, venular dilatation to flicker light seems to be significantly higher. This finding is intriguing, particularly because baseline diameters of both retinal venules and arterioles were not different between the groups. The role of venular retinal dilatation is less understood and has been mainly investigated in patients with end-stage renal disease on haemodialysis, where an impaired venular dilatation has been associated with a worse outcome.[26] However, our study population is not comparable as we investigated stable chronic HF patients under optimal medical therapy. Therefore, our results in respect to venular dilatation remain elusive and warrant further research.

Epicardial adipose tissue and endothelial function in conduit arteries

An increased EAT thickness has been shown to be an independent predictor of endothelial dysfunction measured with FMD (endothelial function in conduit arteries) in patients with cardiovascular risk factors, and an association with inflammatory biomarkers (fibrinogen and high-sensitivity C-reactive protein) has been reported.[27] FMD reflects NO-dependent vasodilation in response to shear stress and represents a well-established parameter to assess macrovascular endothelial function.[28] We found that EAT thickness was an independent predictor of FMD in HFrEF, even after correction for confounding factors as previously discussed (e.g. age, hypertension, dyslipidaemia, and diabetes). Moreover, we found that EAT in patients with HFrEF was related to an increased peripheral arterial stiffness as measured by PWV indicating systemic arterial involvement, which represent a predictor for adverse cardiovascular events.[29] Furthermore, EAT exacerbates oxidative stress and secretes proinflammatory substances such as resistin.[30] These EAT-related atherogenic transcriptomes have been mainly analysed in patients with diabetes and coronary artery disease, while data in patients with HF are missing.[31] All together, these factors may promote systemic atherosclerosis, resulting in increased arterial stiffness and reduced endothelial NO production. Although our data are not sufficient to suggest a mechanistic causation, our study supports the hypothesis of a link between increased EAT and impaired macrovascular function.

Prognostic value of epicardial adipose tissue

After a mean follow-up of >3 years, no clear relationship between EAT and cardiovascular adverse event was found. EAT accumulation yields an adverse prognosis in patients with preserved and mildly reduced ejection fraction in respect to all-cause mortality and HF hospitalization.[8] In contrast, prognostic data on the amount of EAT in HFrEF are sparse.[21]

Limitations

While we acknowledge that this is a single-centre, observational study, we performed regression analyses with correction for clinically relevant confounding factors to investigate the association between EAT and parameters of vascular function. The cohort corresponds to the average distribution of patients, thus resulting in a majority of patients with HFrEF. Accordingly, our HFpEF population is less represented and a lower sample size might have reduced statistical power. Similarly, we had only 32 patients in the HFmrEF group, thus not allowing for reliable regression analyses in this subgroup.

EAT was measured by echocardiography, which may lead to discrimination limitations between EAT and pericardial adipose tissue. Of note, we measured pericardial tissue separately in all patients, thus reducing potential bias.

We found no difference during follow-up in HFrEF patients with reduced EAT thickness as compared with those with an increased EAT thickness, possibly due to the low number of events that occurred during the observation period.

Conclusions

In this study, we demonstrate a diverging role of EAT thickness across the spectrum of HF. First, we report less EAT in HFrEF as compared with HFpEF patients. Second, we found an inverse association between EAT and both retinal vascular function and endothelial function in conduit arteries in HFrEF patients, but not in HFpEF. Thus, the functional phenotype of EAT may be more important for vascular function than the amount of EAT. The diverging role of EAT in HF and its switch to a deleterious tissue promoting HF progression provide the rationale to specifically target EAT in patients with reduced ejection fraction in particular.

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Conflict of interest

A.J.F. declares fees from Alnylam, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Fresenius, Imedos Systems, Medtronic, MSD, Mundipharma, Novartis, Pierre Fabre, Pfizer, Roche, Schwabe Pharma, Vifor, and ZOLL, as well as grant support by Novartis, AstraZeneca, and Berlin Heart unrelated to this article. F.R. has not received personal payments by pharmaceutical companies or device manufacturers in the last 3 years (remuneration for the time spent in activities, such as participation as steering committee member of clinical trials and member of the Pfizer Research Award selection committee in Switzerland, was made directly to the University of Zurich). The Department of Cardiology (University Hospital of Zurich/University of Zurich) reports research, educational, and/or travel grants from Abbott, Amgen, AstraZeneca, Bayer, Berlin Heart, B. Braun, Biosense Webster, Biosensors Europe AG, Biotronik, BMS, Boehringer Ingelheim, Boston Scientific, Bracco, Cardinal Health Switzerland, Corteria, Daiichi, Diatools AG, Edwards Lifesciences, Guidant Europe NV (BS), Hamilton Health Sciences, Kaneka Corporation, Kantar, Labormedizinisches Zentrum, Medtronic, MSD, Mundipharma Medical Company, Novartis, Novo Nordisk, Orion, Pfizer, Quintiles Switzerland Sarl, Roche Diagnostics, Sahajanand IN, Sanofi, Sarstedt AG, Servier, SIS Medical, SSS International Clinical Research, Terumo Deutschland, Trama Solutions, V-Wave, Vascular Medical, Vifor, Wissens Plus, and ZOLL. The research and educational grants do not impact on his personal remuneration. All other authors have no conflict of interest related to the topic of the paper.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Patients with HFrEF due to non-ischemic heart disease vs. patients with HFrEF due to ischemic heart disease.

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