

The Quantity of Epicardial Adipose Tissue in Patients Having Ablation for Atrial Fibrillation With and Without Heart Failure



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The distribution of epicardial adipose tissue (EAT) across the spectrum of heart failure (HF) has yet to be fully elucidated. The present study investigated the distribution of EAT in an HF spectrum and its association with clinical and echocardiographic parameters. A total of 326 patients who underwent contrast-enhanced computed tomography before transcatheter atrial fibrillation ablation with and without HF symptoms, and a wide range of left ventricular (LV) ejection fractions (LVEF) were included. EAT mass was quantified on contrast-enhanced computed tomography using dedicated software. A total of 36 patients had HF with reduced LVEF (HFrEF) (11.0%), 46 had HF with mid-range LVEF (HFmrEF) (14.1%), 53 had HFpEF (16.3%), and 191 did not have HF symptoms (58.6%) and were considered controls. Patients with HFpEF had the largest EAT mass, significantly higher than the control group (128 ± 36 g vs 95 ± 35 g, $p < 0.001$), the HFmrEF group (101 ± 37 g, $p < 0.001$), and the HFrEF group (103 ± 37 g, $p = 0.002$). However, there were no differences in EAT mass between patients with HFrEF, HFmrEF, and controls. EAT was independently associated with E/e', LV mass index, and tricuspid regurgitation velocity. Male gender, body mass index, and C-reactive protein levels were independently associated with EAT. In conclusion, patients with HFpEF had more EAT than patients with HFmrEF, patients with HFpEF, and controls. EAT was associated with worse LV diastolic dysfunction, whereas C-reactive protein levels were independently associated with EAT, suggesting an active inflammatory component. © 2022 The Author (s). Published by Elsevier Inc. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>) (Am J Cardiol 2022;172:54–61)

Epicardial adipose tissue (EAT), which surrounds the myocardium and the coronary arteries, has an important endocrine and inflammatory function.^{1,2} EAT has been shown to secrete proinflammatory adipokines, leading to microcirculatory abnormalities and myocardial fibrosis,³ and has potentially been implicated in the development of atrial fibrillation (AF) and heart failure (HF).⁴ A previous research has reported that patients with HF with a left ventricular (LV) ejection fraction (LVEF) $>40\%$ have increased EAT mass than normal controls.⁵ In contrast, HF with a reduced LVEF (HFrEF) $\leq 40\%$ has been associated with a significant decrease in the volume of EAT compared with healthy controls.⁶ However, the relation between EAT and the entire spectrum of patients with HF has yet to be fully elucidated.

Therefore, the present study aimed to: (1) determine the association between EAT mass quantified in contrast-enhanced computed tomography (CT) and the spectrum of HF; (2) explore the relation between EAT and cardiac structure and function; and (3) evaluate the clinical associates of EAT.

Methods

Patients with AF, with or without HF symptoms, who underwent contrast-enhanced CT before AF ablation between May 2002 and July 2015 at the Leiden University Medical Center (Leiden, The Netherlands) were included. Patients with significant valvular heart disease and with congenital heart disease were excluded. Baseline demographic and clinical data were collected from the Departmental Cardiology Information System (EPD-Vision: Leiden University Medical Center). This retrospective study was approved by the institutional review board and the requirement for written informed consent from patients was waived.

Patients were classified as having HF based on the New York Heart Association functional class II to IV symptoms or a documented history of HF admission (Figure 1). In addition, based on LVEF and current criteria of the European Society of Cardiology guidelines, HF was subclassified as HF with preserved LVEF (HFpEF), HF with mid-

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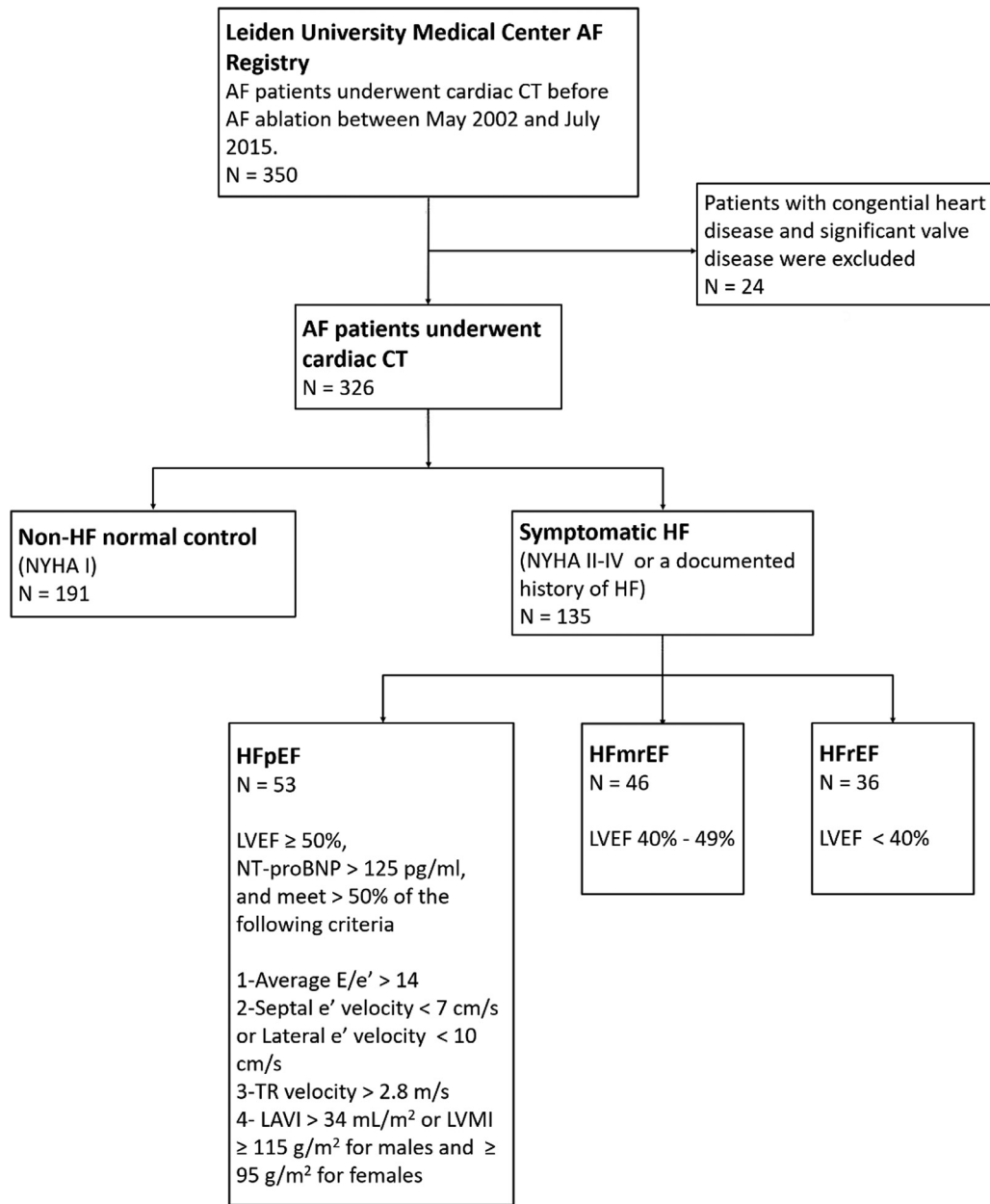


Figure 1. Patient enrollment diagram. NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association; TR = tricuspid regurgitation.

range LVEF (HFmrEF), or HF with reduced LVEF (HFrEF).⁷ The patients without HF symptoms or documented history of HF formed the control group.

Transthoracic echocardiography before AF ablation was performed using a commercially available ultrasound system equipped with 3.5 MHz or M5S transducers (E9 and E95, GE-Vingmed, Horten, Norway). The images were digitally stored and retrospectively analyzed (EchoPAC Version 203.0.1, GE Medical Systems, Horten, Norway). All echocardiographic examinations were performed before AF ablation. LV volumes were measured on the apical 4- and 2-chamber views and LVEF was calculated using the Simpson biplane method.⁸ The left atrial (LA) volume was measured on the apical 4- and 2-chamber views according to the method of disks and indexed to body surface area. LV

internal diameters, ventricular septal thickness, and posterior wall thickness were measured at end-diastole and end-systole. LV mass was calculated based on the formula recommended by the American Society of Echocardiography and the European Association of Cardiovascular Imaging and indexed to body surface area.⁸ The peak velocity of the tricuspid regurgitation jet was measured to calculate right ventricular systolic pressure by the modified Bernoulli equation. Diameter and inspiratory collapsibility of the inferior vena cava were assessed to determine right atrial pressure. Pulsed-wave Doppler of mitral inflow was used to measure LV diastolic function parameters, including peak velocity of the early diastolic (E) and late diastolic (A) waves, and the E/A ratio was calculated. The septal and lateral peak early diastolic mitral annular velocities (e') were

measured with tissue Doppler imaging applied to the apical 4-chamber view. Subsequently, the ratio between peak E wave velocity and e' was calculated to assess LV filling pressures. Using 2-dimensional speckle-tracking echocardiography, LV global longitudinal strain (GLS) was measured in the apical 4-, 2-chamber, and long-axis views with appropriate frame rates.⁹ LVGLS was calculated from the average longitudinal strain curve of the 3 apical views. LA reservoir strain was also evaluated by echocardiographic speckle-tracking strain imaging in the apical 4-chamber view. LA reservoir strain was measured as the peak longitudinal strain during ventricular systole.¹⁰

CT data were acquired using a 64-detector (Aquilion 64, Toshiba medical system, Otawara, Japan) or 320-detector (Aquilion One, Toshiba Medical Systems, Tochigi-ken, Japan) row CT scanners with a dedicated protocol. In brief, β -blockers were used to control the heart rate below 70 beats/min if necessary, unless there were clinical contraindications. According to estimated glomerular filtration rate, weight, and scanning time of the patients, nonionic contrast media, from 60 to 100 ml (Iomeron 400, Bracco, Milan, Italy), was infused in the antecubital vein.

EAT mass was measured on CT data using the MASS software (LKEB, Leiden, The Netherlands) on 2 mm slices, displaying the axial view of the heart and setting the superior and inferior limits at the level of the pulmonary artery bifurcation and the posterior descending coronary artery, respectively.¹¹ The pericardium was manually traced from the pulmonary artery bifurcation until the posterior descending coronary artery. The adipose tissue was automatically identified by the software as tissue with Hounsfield Units between -195 and -45 within the region of the pericardium (Figure 2).

Normally distributed continuous variables are presented as mean $\pm$ SD, and non-normally distributed continuous variables are presented as median and interquartile range. Categorical data were presented as frequencies with percentages. Differences between groups were compared using analysis of variance, Kruskal–Wallis test, t test, Mann–Whitney U test, or chi-square test, as appropriate. EAT mass values were normally distributed. The association between EAT mass and echocardiographic parameters were analyzed using Pearson correlation. A multivariable linear

regression model was used to evaluate whether EAT was independently associated with important parameters of diastolic function. In addition, associations between EAT mass and clinical variables were evaluated with linear regression analysis. The intra- and interobserver variability of EAT measurements were assessed by repeating the measurements in 10 randomly selected patients and calculating the intraclass correlation coefficient. Variables with a $p < 0.05$ on univariable analysis were included in the multivariable analysis. All tests were 2-sided, and $p < 0.05$ were considered statistically significant. Statistical analysis was performed using SPSS for Windows (Version 25.0. SPSS Inc., Chicago, Illinois).

Results

A total of 326 patients with AF who underwent CT before AF ablation were included (mean age 59 ± 9 years, 77% men). The patients were classified into 4 groups: 191 controls (58.6%), 53 with HFpEF (16.3%), 36 with HFmrEF (11.0%), and 46 with HFmEF (14.1%). Clinical characteristics of the patient groups are presented in Table 1. Compared with controls, patients with HFpEF had a larger body mass index (BMI); more often had persistent AF, obstructive sleep apnea syndrome, and previous coronary artery disease; and more frequently used diuretics and angiotensin-converting enzyme inhibitor/angiotensin receptor blocker therapy. In terms of laboratory data, patients with HFpEF had higher N-terminal pro-B-type natriuretic peptide than controls.

Sinus rhythm during the echocardiographic data acquisition was present in 179 patients: 116 in the control group (31%), 31 in the HFpEF group (59%), 19 in the HFmrEF group (41%), and 13 in the HFmEF group (36%). Compared with controls, patients with HFpEF had higher E/e' , larger LV mass index (LVMI), and higher tricuspid regurgitation velocity (TRV), and more impaired LA reservoir strain (Table 2). There were no significant differences between patients with HFpEF and the control group in terms of LVEF and LVGLS. Patients with HFpEF had significantly larger EAT mass than the other groups. In contrast, there was no significant difference in terms of EAT mass between the HFmrEF group, the HFmEF group, and the control group.

Based on Pearson correlation coefficient analysis, EAT mass was significantly associated with cardiac diastolic function parameters such as E/e' ($R = 0.149$, $p = 0.007$), LVMI ($R = 0.173$, $p = 0.002$), and peak TRV ($R = 0.129$, $p = 0.022$) (Figure 3). In contrast, there was no significant correlation between EAT and LVEF and LVGLS (Supplementary Table 1). After multivariable adjustment for age, gender, BMI, and co-morbidities, EAT remained independently associated with diastolic function parameters including E/e' , LVMI, and peak TRV (Table 3). In addition, ventricular septum thickness and posterior wall thickness were positively associated with EAT mass ($R = 0.198$, $p < 0.001$ and $R = 0.233$, $p < 0.001$, respectively), whereas LV end-diastolic and LV end-systolic volumes were negatively associated with EAT mass. There was no significant

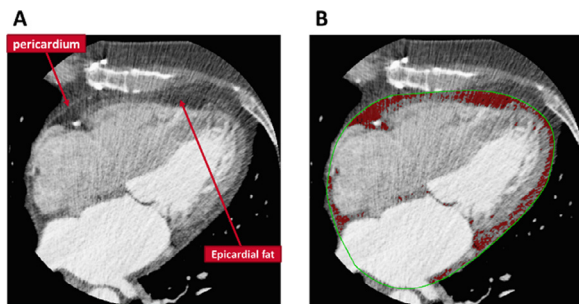


Figure 2. Measurement of epicardial adipose tissue mass. Panel A shows the identification of the pericardium and the epicardial fat tissue. Manual tracing was performed on the four-chamber view at different levels from the right pulmonary artery to the diaphragm and the adipose tissue within the pericardium was included. Adipose tissue was automatically recognized by the software as tissue with Hounsfield Units between -195 and -45 (panel B).

Table 1
Patient characteristics

Variable	Control (n=191)	HFpEF (n=53)	HFmrEF (n=46)	HFrfEF (n=36)	p- Value
Clinical variables					
Age, years	56.7 ± 9.1	58.5 ± 8.7	57.4 ± 11.0	57.6 ± 8.7	0.668
Male sex	143 (74.9%)	43 (81.1%)	36(78.3%)	30 (83.3%)	0.602
Body mass index, kg/m ²	27.0 ± 3.6*	28.8 ± 5.1 [†]	26.1±3.2	27.7 ± 3.6	0.003
Body surface area, m ²	2.1±0.2	2.1±0.2	2.0±0.2	2.1±0.2	0.045
Persistent atrial fibrillation	85 (44.5%)*,†,‡	32 (60.4%)	28(60.9%)	20(55.6%)	0.067
Atrial fibrillation burden, %	35.6±45.3 ^{†,‡}	48.5±48.3	52.1±48.1	54.7±47.7	0.040
Smoking	16 (8.4%) ^{†,§}	4 (7.5%)	9(19.6%)	5 (13.9%)	0.005
Co-morbidities					
Hypertension	122 (63.9%)	39 (73.6%)	24(52.2%)	22 (61.1%)	0.174
Diabetes mellitus	9 (4.7%)	5 (9.4%)	4(8.7%)	3 (8.3%)	0.505
Hypercholesterolemia	56 (29.3%)	23 (43.4%)	16(34.8%)	13 (36.1%)	0.264
Coronary artery disease	16 (8.4%)*,†,‡	11(20.8%)	10(21.7%)	10(27.8%)	0.002
Obstructive sleep apnea syndrome	3 (1.6%)	7 (13.5%)	2 (4.3%)	0	<0.001
Medication					
Diuretics	19 (9.9%)*,†,‡	20 (37.7%)	15 (32.6%)	8 (22.2%)	<0.001
ACE-I/ARB	79 (41.4%)*	36 (67.9%)	24 (52.2%)	17 (47.2%)	0.007
Calcium channel blockers	32 (16.8%)	12 (22.6%)	7(15.2%)	8(22.2%)	0.650
Beta blockers	116 (60.7%)	37 (69.8%)	27(58.7%)	27(75.0%)	0.256
Laboratory data					
Total cholesterol, mmol/L	5.3 ± 1.2	5.1 ± 0.9	5.2 ± 1.0	4.9 ± 1.4	0.336
Triglycerides, mmol/L	1.9 ± 1.1	2.1 ± 1.0	2.1 ± 1.2	1.9 ± 0.9	0.671
Thyroxine, ug/dl	17.9 ± 5.1	17.0 ± 2.4	17.0 ± 2.4	17.4 ± 3.2	0.523
TSH, mU/L	2.9 ± 5.4	2.6 ± 1.7	2.4 ± 3.2	2.3 ± 1.4	0.851
Creatinine, mmol/L	82.5 ± 16.6	87.4 ± 27.1	84.0 ± 16.8	86.8 ± 16.1	0.298
NT-proBNP, ng/L	100 (65-180)*,†,‡	709 (588-849)	880(484-1511)	1207(582-1860)	0.001
C-reactive protein, mg/L	3.0 ± 12.1*,†	11.2 ± 27.1	2.8 ± 3.8	9.0 ± 28.5	0.007

Values are mean ± standard deviation if normally distributed and median (interquartile range) if not normally distributed.

ACE-I = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; HFmrEF = heart failure with mid-range ejection fraction; HFpEF = heart failure with preserved ejection fraction; HFrfEF = heart failure with reduced ejection fraction; NT-proBNP = N-terminal pro-B-type natriuretic peptide; OSAS = obstructive sleep apnea syndrome; TSH = thyroid stimulating hormone.

* Compared with HFpEF group, p value <0.05.

† Compared with HFmrEF group, p value <0.05.

‡ Compared with HFrfEF group, p value <0.05.

correlation between EAT mass and LAVI (Supplementary Table 1).

To investigate the association of various clinical parameters with the extent of EAT, univariable and multivariable linear regression analysis were conducted. In univariable analysis, male gender, BMI, hypertension, obstructive sleep apnea syndrome, triglycerides, creatinine, and C-reactive protein (CRP) levels were significantly associated with EAT mass (Table 4). In multivariable linear regression model, male gender, BMI, and CRP levels remained independently associated with EAT mass after adjusting for covariates (B 25.796, p <0.001; B 2.526, p <0.001; and B 19.869, p <0.001, respectively) (Table 4).

The interobserver and intraobserver variabilities of the EAT measurement were good, with an intraclass correlation coefficient of 0.982 (95% confidence interval 0.921 to 0.995) and 0.990 (95% confidence interval 0.962 to 0.997), respectively.

Discussion

The association between EAT and the presence of HF has been described in various studies. In 64 patients with HF with LVEF >40%, Van Woerden et al⁵ demonstrated a

significantly larger EAT mass than normal controls. In contrast, in 66 patients with HFrfEF who underwent CT, the EAT mass was significantly lower than healthy controls.⁶ In the present study, patients with HFpEF had the largest amount of EAT, which was significantly larger than that in other patient groups. HFrfEF typically occurs as the result of cardiomyocyte damage, caused by acute or chronic myocardial ischemia, a genetic mutation, myocarditis, or valvular disease; whereas HFpEF is often preceded by systemic comorbidities and proinflammatory diseases (such as obesity, diabetes, hypertension, or auto-immune diseases). Accordingly, biomarker profiles in HFrfEF were predominantly correlated with myocardial stretch, whereas in HFpEF correlated with inflammation.^{12,13} An intermediate biomarker profile was displayed in patients with HFmrEF, as biomarker interactions between both myocardial stretch and inflammation biomarkers have been described.¹³ The associations between EAT and CRP observed in the present study support the hypothesis that EAT may serve as an important mediator between systemic inflammation and HFpEF.

In the present study, EAT was associated with echocardiographic parameters of LV diastolic function; however, in contrast to previous studies, there was no relation

Table 2
Imaging variables

Variable	Control (n=191)	HFpEF (n=53)	HFmrEF (n=46)	HFrfEF (n=36)	p-Value
Echocardiographic parameters					
Interventricular septum thickness, mm	11.8 ± 2.2	12.3 ± 2.8	12.0 ± 2.4	12.0 ± 2.4	0.485
Posterior wall thickness, mm	10.7 ± 3.6	11.2 ± 2.2	11.1 ± 2.2	12.9 ± 2.9	0.174
Left ventricular end-diastolic volume, ml	103.1 ± 32.1*	103.2 ± 41.0	102.7 ± 43.4	125.8 ± 54.1	0.023
Left ventricular end-systolic volume, ml	41.2 ± 15.5* [†]	42.5 ± 25.7	48.3 ± 22.0	75.2 ± 45.9	<0.001
Left ventricular ejection fraction, %	60.3 ± 6.4* [†]	59.7 ± 7.8* [†]	45.0 ± 2.6*	33.9 ± 6.9	<0.001
Left ventricular global longitudinal strain, %	-16.5 ± 5.1* [†]	-16.3 ± 3.8* ^{†,§}	-14.7 ± 4.0	-11.7 ± 3.8	<0.001
Left atrial reservoir strain, %	25.4 ± 17.4* [†]	21.8 ± 10.5* [†]	17.0 ± 9.3	13.4 ± 9.5	<0.001
Left ventricular mass index, g/m ²	96.1 ± 29.3* ^{†,‡}	107.7 ± 30.4*	110.9 ± 32.6	120.9 ± 37.5	<0.001
e', cm/s	9.1 ± 1.8* ^{†,‡}	8.8 ± 1.9*	8.2 ± 2.1*	7.2 ± 1.8	<0.001
E/e'	8.7 ± 3.5 * ^{†,‡}	12.0 ± 6.1	11.1 ± 4.6 *	14.22 ± 8.2	<0.001
E/A	1.9 ± 0.5	1.4 ± 0.9	1.8 ± 0.8	1.9 ± 0.9	0.999
Tricuspid regurgitation peak velocity, m/s	2.2 ± 0.5 * ^{†,‡}	2.4 ± 0.6	2.5 ± 0.4	2.6 ± 0.4	<0.001
Left atrial volume index, ml/m ²	41.4 ± 16.1	44.9 ± 19.3	45.7 ± 18.7	45.7 ± 19.8	0.252
Computed tomography parameter					
Epicardial adipose tissue, g	95 ± 35 [‡]	128 ± 36* [†]	101 ± 37	103 ± 37	<0.001

Values are mean ± standard deviation if normally distributed and median (interquartile range) if not normally distributed.

E = peak early diastolic mitral flow velocity; e' = peak early diastolic mitral annular tissue velocity; HFmrEF = heart failure with mid-range ejection fraction; HFpEF = heart failure with preserved ejection fraction; HFrfEF = heart failure with reduced ejection fraction.

* Compared with HFrfEF group, p<0.05.

[†] Compared with HFmrEF group, p<0.05.

[‡] Compared with HFpEF group, p<0.05.

between EAT and LAVI, another diastolic dysfunction parameter.⁷ In patients with AF, LAVI is a less reliable indicator of LV diastolic function because of the frequent occurrence of LA dilation regardless of LV filling pressures.¹⁴ In addition to the systemic influence of obesity and visceral adipose tissue on the cardiovascular system, the local effects of EAT should not be ignored. The proinflammatory mediators secreted by EAT may exert local toxic effects on the adjacent myocardium, impairing the chamber's distensibility and increasing diastolic stiffness

and LV filling pressures.¹⁵ Subclinical impairment of LV function may be a precursor to the onset of symptomatic cardiac dysfunction and HF. It is worth noting that systolic function can be compromised by the myocardial inflammatory process, although LVEF is generally preserved in these patients.¹⁶

EAT was associated with BMI in the present study, which is consistent with previous reports.^{17,18} The correlation between obesity and HF has been well established.¹⁹ Recently, obesity-related HFpEF was proposed and

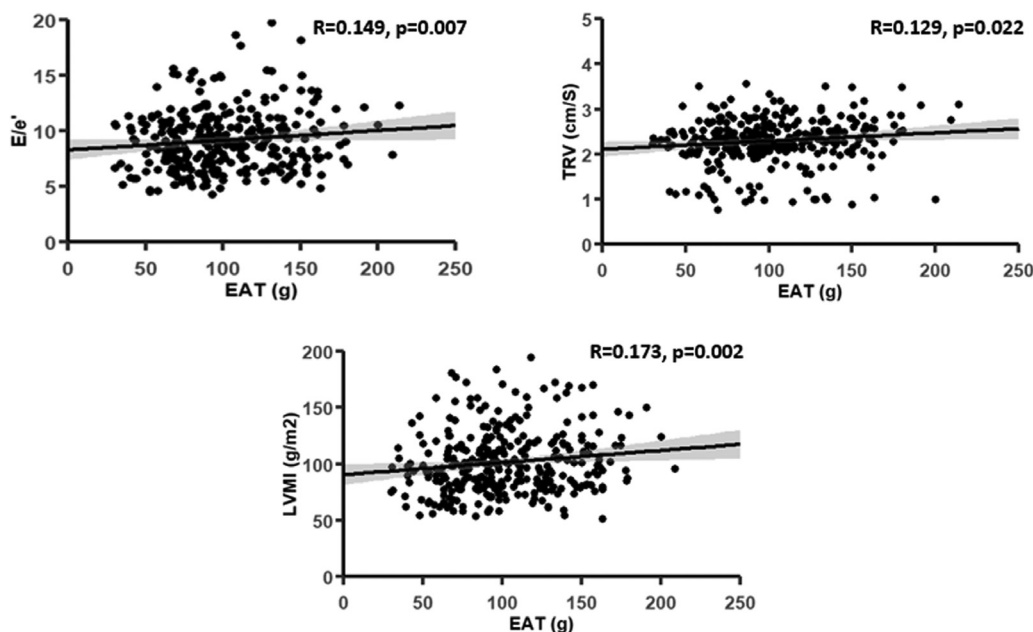


Figure 3. Association between EAT mass and echocardiographic diastolic dysfunction parameters. Scatter plots of EAT and echocardiographic E/e', LVMI and TRV (A, B, and C, respectively).

Table 3

Multivariable linear regression for epicardial adipose tissue and echocardiographic diastolic parameters

Echocardiographic parameters	Epicardial adipose tissue (g)	
	Adjusted B* (95% CI)	P-value
E/e'	0.019 (0.003 to 0.035)	0.021
Left atrial volume index, ml/m ²	0.010 (-0.049 to 0.068)	0.745
Left ventricular mass index, g/m ²	0.150 (0.044 to 0.255)	0.006
Tricuspid regurgitation peak jet velocity, m/s	0.003 (0.001 to 0.004)	<0.001

CI = confidence interval; E = peak early diastolic mitral flow velocity; e' = peak early diastolic mitral annular tissue velocity.

* Adjusted age, sex, body mass index, diabetes, and hypertension.

considered to be a distinct phenotype within the HF spectrum.¹⁵ Of note, different fat depots may be associated with particular metabolic risk factors and confer increased risk beyond overall body fat indicators such as BMI and waist circumference.^{20,21} Regional visceral adipose tissue including pericardial fat and visceral abdominal have been shown to be associated with cardiovascular risk, and this association was independent of total adiposity.²²

There is growing evidence that adipose tissue and the corresponding inflammation may play an important role in the pathogenesis of HFpEF.^{15,23} Adipose tissue is now recognized as an endocrine organ, which can produce and secrete proinflammatory adipokines that contribute to an inflammatory burden.²⁴ EAT exhibits significantly greater inflammatory responses than subcutaneous fat in patients with high cardiovascular risk. Moreover, inflammation associated with EAT has been shown to be independent of obesity or diabetes.² Adipocyte-expressed interleukin-6 induces low-grade systemic inflammation and directly stimulates hepatic synthesis of CRP.^{25,26} Additionally, adipose tissue itself can be a source of CRP.²⁷ Furthermore, EAT may exert a direct effect on adjacent myocardium by releasing proinflammatory adipokines. This local inflammatory

process may lead to microcirculatory dysfunction and fibrosis of myocardium, which may contribute to the development of LV diastolic dysfunction and HF.^{16,28,29}

This study has all of the inherent limitations associated with a single-center, retrospective design and the large time span of the study (10 years). Even though AF might be a sign of the presence of HFpEF, N-terminal pro-B-type natriuretic peptide, and LAVI are usually increased in patients with AF, which may lower the diagnostic value of these parameters in patients with HFpEF. In particular, LAVI may not accurately reflect the LV diastolic function in the setting of AF.⁷ Furthermore, CT data acquisition and analysis in patients in AF may be challenging. The weak relation between EAT and overall body fat may be enhanced if regional obesity measures such as waist circumference or waist:hip ratio are used instead of BMI.

Disclosures

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Table 4

Univariable and multivariable linear regression analysis for determinants of epicardial adipose tissue

Variable	Epicardial adipose tissue (g)			
	Univariable linear regression		Multivariable linear regression	
	B coefficient	P-value	B coefficient	P-value
Age, years	0.289	0.196		
Male sex	24.713	<0.001	25.796	<0.001
Body mass index, kg/m ²	3.173	<0.001	2.526	<0.001
Heart rate, bpm	0.135	0.200		
Persistent atrial fibrillation	2.768	0.503		
Atrial fibrillation burden, %	0.046	0.332		
Hypertension	11.270	0.008	5.368	0.207
Diabetes mellitus	2.719	0.747		
Coronary artery disease	5.014	0.394		
Obstructive sleep apnea	36.883	0.001	19.869	0.061
Laboratory data				
Total cholesterol, mmol/L	-0.872	0.663		
Triglycerides, mmol/L	6.249	0.004	2.673	0.168
Thyroxine, ug/dl	0.132	0.801		
TSH, mU/L	-0.214	0.672		
C-reactive protein > 3 mg	23.861	<0.001	19.869	<0.001
NT-proBNP, ng/L	0.013	0.290		
Creatinine, mmol/L	0.236	0.032	-0.101	0.445

NT-proBNP = N-terminal pro-B-type natriuretic peptide; TSH = thyroid stimulating hormone.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at <https://doi.org/10.1016/j.amjcard.2022.02.021>.

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