Cardiovascular Diabetology

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Exploring the impact of metabolic comorbidities on epicardial adipose tissue in heart failure with preserved ejection fraction

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Abstract

Background Heart failure (HF) with preserved ejection fraction (HFpEF) is increasingly prevalent worldwide due to aging and comorbidities. Epicardial adipose tissue (EAT), favored by diabetes and obesity, was shown to contribute to HFpEF pathophysiology and is an emerging therapeutic target. This study explored the relationship between ventricular EAT measured by cardiovascular magnetic resonance (CMR), metabolic factors, and imaging characteristics in controls, pre-HF patients, and HFpEF patients.

Methods Patients from a Belgian cohort enrolled from December 2015 to June 2017 were categorized by HF stage: pre-HF (n = 16), HFpEF (n = 104) and compared to matched controls (n = 26) and to pre-HF (n = 191) from the Beta3-LVH cohort. Biventricular EAT volume was measured in end-diastolic short-axis cine stacks. In the Belgian cohort, associations between EAT, HF stage, and various biological and imaging markers were explored. The clinical endpoint was a composite of mortality or first HF hospitalization in the HFpEF group.

Results EAT significantly differed between groups, with higher values in HFpEF patients compared to pre-HF and controls ($72.4 \pm 20.8 ml/m^2$ *vs.* $55.0 \pm 11.8 ml/m^2$ and $48 \pm 8.9 ml/m^2$, $p < 0.001$) from the Belgian cohort and to pre-HF (52.0 ± 15.0 ml/m^2, $p < 0.001$) from the Beta3-LVH cohort. Subsequent analyses focused on the Belgian cohort. In

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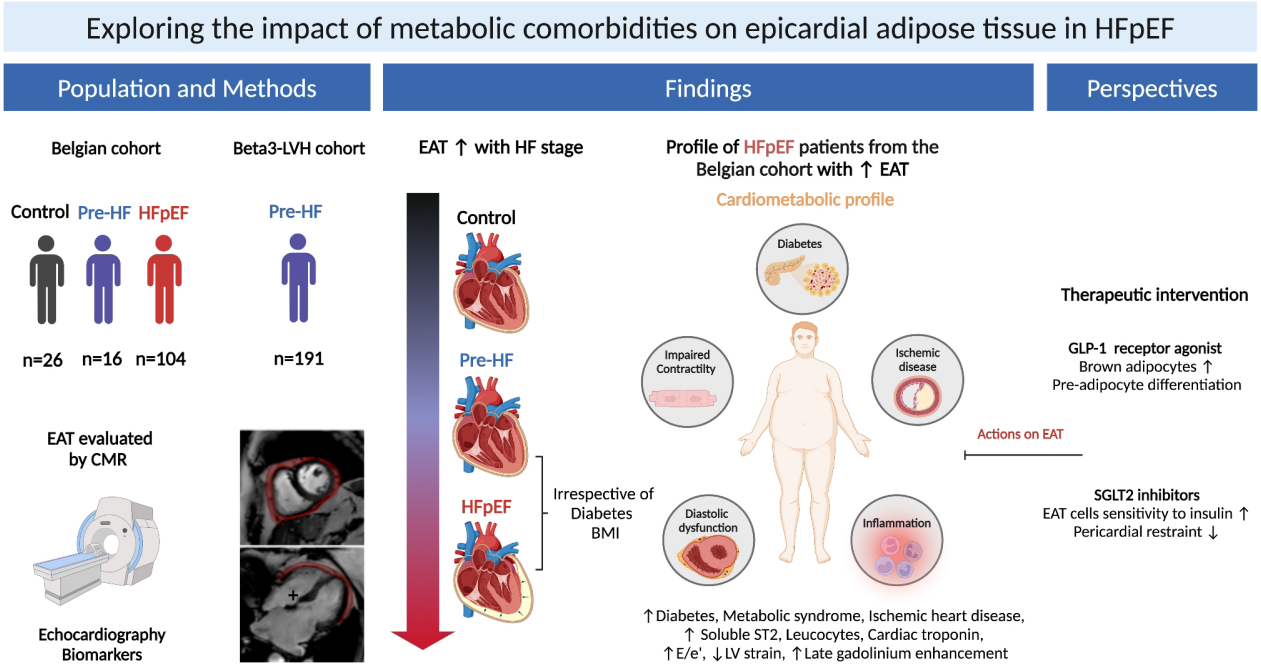
contrast to atrial fibrillation, diabetes prevalence and body mass index (BMI) did not differ between pre-HF and HFpEF patients. Multivariable logistic regression and random forest classification identified EAT, N-terminal pro-B-type natriuretic peptide (NT-proBNP), and H_2FPEF score as strong markers of HFpEF status. EAT was significantly correlated with H_2FPEF score ($r=0.41$, $p=0.003$), BMI ($r=0.30$, $p<0.001$), high-sensitive troponin T ($r=0.41$, $p<0.001$), NT-proBNP ($r=0.37$, $p<0.001$), soluble suppression of tumorigenicity-2 (sST2) ($r=0.30$, $p<0.001$), E/e' ratio ($r=0.33$, $p<0.001$), and left ventricular global longitudinal strain ($r=0.35$, $p<0.001$). In HFpEF patients, diabetes, ischemic cardiomyopathy, and elevated sST2 were independently associated with elevated EAT. In contrast with diabetes and BMI, increased EAT was not associated with prognosis.

Conclusions EAT assessed by CMR was significantly higher in HFpEF patients compared to controls and pre-HF patients, irrespective of diabetes and BMI. EAT was moderately associated with HFpEF status. HFpEF patients with elevated EAT exhibited a marked diabetic, ischemic, and inflammatory profile, highlighting the potential role of drugs targeting EAT.

Trial registration Characterization of Heart Failure With Preserved Ejection Fraction; Assessment of Efficacy of Mirabegron, a New beta3-adrenergic Receptor in the Prevention of Heart Failure (Beta3_LVH).

Trial registration number ClinicalTrials.gov. Identifier: NCT03197350; NCT02599480.

Graphical abstract



Keywords Epicardial adipose tissue, Heart failure with preserved ejection fraction, Diabetes, Obesity, Metabolic syndrome, Inflammation, Cardiovascular magnetic resonance (CMR), Soluble ST2

Background

Heart failure (HF) with preserved ejection fraction (HFpEF) is becoming the most prevalent form of HF worldwide due to an aging population and increasing obesity. Its pathophysiology is complex, triggered by multiple metabolic comorbidities among which type 2 diabetes mellitus (T2DM) and obesity, especially visceral adipose tissue (VAT) accumulation, have been identified to play a central role by creating a chronic low-grade systemic inflammatory state called metainflammation [1].

Epicardial adipose tissue (EAT), a metabolically active VAT in direct contact with the myocardium beneath the visceral pericardium, has recently received increasing attention for its potential role in the pathophysiology of HFpEF [2, 3]. Systemic inflammation is recognized as a critical pathological mechanism in HFpEF with T2DM and obesity. This inflammation contributes to the expansion and dysfunction of EAT, resulting in increased inflammation and hypermetabolic activity within the EAT [4]. According to the adipose tissue hypoxia concept,

excess EAT can progress from healthy to hypertrophic and inflamed tissue, leading to functional impairment of the adjacent cardiac structure based on two complementary hypotheses [5]. First, EAT may directly infiltrate the myocardium and secrete pro-inflammatory adipokines that induce myocardial remodeling via a paracrine pathway, which supports the infiltrative-lipotoxic hypothesis. Second, according to the pericardial restraint hypothesis, excess EAT may directly compress the myocardium as it accumulates in the poorly distensible pericardium, leading to a constrictive pericarditis-like situation [6].

Recent studies have consistently shown that EAT volume is increased in HFpEF patients [5], independent of body mass index (BMI) [7], and that EAT accumulation may predict a worse prognosis [8]. More interestingly, EAT abundance is associated with new-onset HFpEF in the general population [9–11]. Indeed, EAT excess is associated with structural and functional features typically seen in HFpEF patients, such as diastolic dysfunction, myocardial hypertrophy, left atrial (LA) enlargement, and increased filling pressures [5, 12]. These findings support that EAT may play an independent role in the pathogenesis of HFpEF and may represent a novel potential therapeutic target.

However, no previous study has evaluated EAT levels and the influence of comorbidities such as diabetes and obesity across the different stages of a HFpEF cohort using the international definition and classification of HF (preclinical HF or stage B, representing structural heart disease without symptoms, *vs.* HFpEF or stage C, representing structural heart disease with symptoms) [13]. The transition from the asymptomatic pre-HF stage to symptomatic HFpEF typically involves several mechanisms, primarily LA dilatation with atrial fibrillation (AF), right ventricular dysfunction, and renal failure [14]. However, the role of EAT and metabolic factors in this transition is not well described and understood.

In this study, we measured EAT volume using cardiovascular magnetic resonance (CMR) imaging in preclinical HF patients (stage B), HFpEF patients (stage C), and age- and sex-matched controls. We investigated the relationships between ventricular EAT, metabolic factors, and imaging characteristics in these subjects. We also explored the impact of diabetes in HFpEF patients with increased EAT and analyzed how the interplay between diabetes, obesity, and EAT affects the clinical outcome in symptomatic patients.

Methods

Belgian cohort

This study included patients from a Belgian cohort described in a previous study [15]. In brief, consecutive patients with HFpEF (pre-HF and HF stage) were prospectively evaluated for inclusion in the study at a single center in Brussels between December 2015 and June 2017.

HFpEF patients (stage C) had to meet the following criteria to be included in the study: New York Heart Association (NYHA) functional class ≥ II, typical symptoms and signs of HF, N-terminal pro-brain natriuretic peptide (NT-proBNP) > 350 pg/mL, and/or hospitalization for HF in the previous 12 months, with preserved left ventricular (LV) ejection fraction (≥ 50%; HFpEF) and relevant structural heart disease (LV hypertrophy/LA enlargement), and/or diastolic dysfunction assessed by echocardiography for HFpEF, as previously described [15]. For pre-HF (stage B), patients were identified has having no current or previous symptoms or signs of HF, with evidence of structural heart disease according to the universal definition and classification of HF [13]. The exclusion criteria for all patients with pre-HF and HFpEF were severe valvular disease, infiltrative or hypertrophic cardiomyopathy, acute coronary syndrome in the previous 30 days, chronic obstructive pulmonary disease global initiative for obstructive lung disease (GOLD) 3 or 4, congenital heart disease, pericardial disease, terminal renal failure with estimated glomerular filtration rate (eGFR) < 15 mL/min/1.73 m^2 or subjects requiring dialysis, atrial fibrillation with a ventricular response > 140 bpm, severe anemia (hemoglobin < 8 g/dL), cirrhosis, and active cancer.

A total of 157 patients with HFpEF were recruited and underwent CMR imaging. Of the 157 HFpEF patients initially identified, 53 were excluded from the analysis (Figure S1in Additional file 1); however, comparisons of clinical, imaging, and biochemical characteristics between included (n = 104) and excluded (n = 53) patients revealed no significant differences, suggesting that their exclusion is unlikely to have introduced bias into the study's findings (Table S1 in Additional file 1). Finally, 104 HFpEF patients and 16 age- and sex-matched pre-HF patients underwent biventricular EAT measurement.

Patients were compared with age- and sex-matched controls (n = 26) with no history of cardiovascular disease, significant medical history, or chronic disease. All controls were recruited by advertisement in the local community and underwent a clinical examination, electrocardiogram, echocardiography, CMR, and exercise stress test, all of which had to be normal prior to inclusion.

Patients and controls underwent blood sampling, complete transthoracic echocardiography, and CMR in the absence of the following contraindications: pacemaker, claustrophobia, or eGFR (eGFR) < 30 mL/min/1.73m^2.

The H_2FPEF score, a tool to assess the diagnostic likelihood of HFpEF, was calculated for all participants. It includes several parameters: obesity, hypertension, AF, pulmonary hypertension, age > 60 years, and E/e' ratio > 9 (Table S2 in Additional file 1) [16]. Metabolic score was

calculated using the following criteria: hypertension, obesity (BMI ≥ 30 kg/m^2), hypercholesterolemia according to sex, hypertriglyceridemia, hyperglycemia. Metabolic syndrome was defined as a metabolic score > 3.

The study adhered to the tenets of the Declaration of Helsinki. The local ethics committee approved the study protocol and all patients provided written informed consent prior to enrollment (Clinical trial NCT03197350).

All subjects underwent complete two-dimensional transthoracic echocardiography (iE33 system, Philips Healthcare, Best, The Netherlands) at inclusion to assess LV and right ventricular structure, systolic and diastolic function, LA and right atrial (RA) volumes, and valvular status. Pulmonary pressures were estimated from tricuspid regurgitation velocity. Strain analysis was performed on acquired images of acceptable quality using TOMTEC software (Munich, Germany). All echocardiographic measurements were averaged over three beats in case of AF.

Blood samples were collected by venipuncture at inclusion. After centrifugation at 3500 rpm for 10 min, aliquots of serum and plasma were stored at − 80 °C. High-sensitive troponin T (hsTnT) and NT-proBNP were measured by two-site electrochemiluminescence immunoassay on the Cobas 8000 platform (Roche Diagnostics, Mannheim, Germany). C-terminal fibroblast growth factor-23 (cFGF-23) concentrations were determined by a second-generation human C-terminal enzyme-linked immunosorbent assay (Immutopics, San Clemente, CA, USA). Soluble suppression of tumorigenicity-2 (sST2) was measured using the Presage® ST2 enzyme-linked immunosorbent assay (Critical Diagnostics, CA, USA). The TyG index, a biomarker reflecting insulin resistance, was computed using the following formula: TyG index = ln [fasting triglyceride (mg/dl) × fasting glucose (mg/dl)]/2 [17].

HFpEF patients were followed prospectively via outpatient visits and telephone calls at 6-month intervals. Clinical and survival status was obtained through follow-up visits and telephone contact with patients, their relatives, or their physician. The endpoint was a composite of all-cause mortality or hospitalization for HF, whichever came first. Hospitalization was defined as patients treated in an emergency department or admitted to a hospital, diagnosed with decompensated HF, and requiring intravenous diuretics.

Beta3-LVH cohort for confirmation

Beta3-LVH cohort is a European multicentre, randomized, double-blind trial, which took place between September 2016 and February 2021 [18, 19]. It aimed to evaluate the impact of the beta-3 receptor agonist mirabegron on LV mass indexed by CMR and diastolic function (E/e' ratio) in patients with LV hypertrophy. The study enrolled 296 subjects across 10 European centers in 8 countries and followed them over 12 months. Patients aged 18 years or older were screened for the presence of LV hypertrophy (increased LV mass index [LVMI] of ≥ 95 g/m2 for women or ≥ 115 g/m2 for men) or maximum wall thickness of 13 mm or greater using echocardiography. The key inclusion criteria were LV hypertrophy, indicating structural heart disease, and controlled arterial hypertension. All patients with an EF of less than 50%, history of hospitalization for overt HF within last 12 months were also excluded. Patients were considered as pre-HF. Of the 296 subjects, CMR images of 191 were analysed for EAT quantification. The remainder of the methodology, including the exclusion criteria, imaging procedures, and biomarker analysis, has been previously described [18, 19].

Cardiovascular magnetic resonance analysis in the Belgian and the Beta3-LVH cohorts

Each participant underwent CMR imaging using a 1.5 T or 3 T system, with acquisition left to the discretion of the operators, subject to homogeneity dictated by the purpose of the study and the relevance of the images. The quality of the images was checked by the central laboratory. The various sequences have been described previously [20]. After retrieval of the CMR images, biventricular EAT was measured from the basal slice corresponding to the mitral annulus to the most apical slice. Short-axis delineation was verified by matching the four-chamber slice (Figure S2 in Additional file 1). EAT was expressed in volume (mL) and calculated using the Simpson's method by summing all volumes obtained on the short-axis sections. EAT was indexed to the body surface area. All measurements were performed by the same operator for each cohort (ML, MP) and were visually checked by two other experienced operators (NM and BG). In a random sample of subjects, the reproducibility of EAT end-diastolic volume (EDV) was assessed by two independent operators; intraobserver and interobserver agreement was good, with an intraclass correlation coefficient (ICC) of 0.85 and 0.98, respectively. In the Belgian cohort, pre- and post-contrast modified look-locker inversion recovery images were processed using the open-source software MRmap Version 1.4 17 under the Interactive Data Language® software. The extracellular volume (ECV) and late gadolinium enhancement (LGE) were assessed following the methodology previously detailed in the Belgian cohort [20].

Statistical analysis

Statistical analyses were performed using R Version 4.1.2 software (http://www.r-project.org) and Graphpad PRISM. All tests were two-sided, with statistical significance set at $p < 0.05$. Continuous variables were expressed

as mean ± 1 standard deviation if normally distributed or as median and interquartile range (25th and 75th percentiles) if not normally distributed. Normality of a continuous distribution was assessed using skewness and kurtosis statistics. Categorical variables were expressed as counts and percentages. Biomarker levels were log-transformed to establish normality. Comparison between groups was performed using ANOVA with Tukey's or Dunnett's post-hoc analysis, Kruskall-Wallis test, or Chi-square test, as appropriate.

The groups of the Belgian cohort were matched for age and sex. We conducted an ANCOVA analysis to compare EAT between pre-HF in the Beta3-LVH cohort and the subject from the Belgian cohort, adjusting for age, sex and cohort effect. To assess whether EAT is significantly associated with HFpEF status, a logistic regression analysis was conducted in both cohorts. Group differences were accounted for by including cohort as an interaction variable in the model, along with adjustments for clinical parameters that varied between the cohorts.

In the Belgian cohort, we ran two machine learning algorithms to identify factors associated of HFpEF status in the whole population using univariable logistic regression ($p < 0.10$) followed by multivariable logistic regression ($p < 0.05$) and random forest classification analysis (*randomForest package*). To assess the ability of the EAT measurement to identify HFpEF patients, it was tested with all clinical, iconographic, and biological variables. Variables with collinearity ($R > 0.50$ or Variance Inflation Factor (VIF) > 4) were excluded for both analyses. Correlations between EAT and biomarkers were assessed using Pearson's correlation coefficient.

The HFpEF population from the Belgian cohort was divided into two groups according to the median indexed EAT. Comparison between groups was performed using independent samples t-test, Mann–Whitney U test, or Chi-square test, as appropriate; $p < 0.05$ was considered statistically significant. Univariable analysis ($p < 0.10$) and multivariable linear regression ($p < 0.05$) were performed to identify parameters associated with elevated indexed EAT volume in HFpEF patients. Event-free survival of HFpEF patients was estimated using the log-rank test and Cox regression analysis. Kaplan–Meier curves based on the elevated indexed EAT volume group were used to illustrate the composite endpoint.

The ICCs were calculated using a two-way random-effects model to assess absolute agreement (ICC(2,1)).

Results

Baseline characteristics of the Belgian cohort

A total of 104 consecutive HFpEF patients (stage C) (77 ± 8 years; 55% female), 16 pre-HF patients (stage B) (75 ± 4 years; 62% female), and 26 age- and sex-matched controls (76 ± 5 years; 63% female) were prospectively included in the study. Baseline patient characteristics are summarized in Table 1. Compared to controls, HFpEF patients had a higher incidence of cardiovascular risk factors and comorbidities such as diabetes, obesity, hypertension, and ischemic cardiomyopathy. These patients had lower hemoglobin levels and lower eGFR. Median NT-proBNP, neutrophil count, hsTnT, C-reactive protein (CRP), cFGF-23, and sST2 levels were significantly higher in HFpEF patients. Echocardiography showed higher LA and RA volumes, indexed LV EDV, E/e′ ratio, and pulmonary pressures, and lower E deceleration time, tricuspid annular plane systolic excursion (TAPSE), and fractional area change. Regarding CMR parameters, HFpEF patients had significantly higher indexed ventricular EAT volume compared to controls (72 ± 20.8 ml/m^2 *vs.* 48.0 ± 8.9 ml/m^2, $p < 0.001$), as well as higher LA volume, indexed LV EDV, indexed LV end-systolic volume, extracellular volume (ECV), and late gadolinium enhancement (LGE) than controls (Fig. 1).

As expected, controls differed from pre-HF patients mostly in terms of history of ischemic cardiomyopathy, NT-proBNP levels, and echocardiographic markers indicating elevated filling pressure (E/A ratio, E/e'ratio, indexed LA volume, and pulmonary pressures). There was no significant difference in EAT levels between controls and pre-HF patients (48.0 ± 8.9 ml/m^2 *vs.* 55.0 ± 11.8 ml/m^2, $p = 0.46$) (Fig. 1).

According to the definition of HF stages, HFpEF patients differed from pre-HF patients mainly in terms of symptoms (NYHA class), NT-proBNP levels, H_2FPEF score (Fig. 2A, score calculation in Table S2 in Additional file 1), and diuretic use, whereas echocardiographic parameters of diastolic dysfunction and pulmonary pressure did not differ. They also had higher levels of inflammatory biomarkers (sST2) and myocardial injury markers (hsTnT), larger indexed LA volumes with more frequent AF, poorer global systolic function (with significantly lower TAPSE, LV global longitudinal strain [GLS], and LV ejection fraction [LVEF] as assessed by CMR), and increased markers of myocardial fibrosis (with higher ECV and LGE). HFpEF patients exhibited a significantly higher indexed EAT volume (72.4 ± 20.8 ml/m^2 *vs.* 55.0 ± 11.8 ml/m^2, $p = 0.002$) (Fig. 1), with no significant difference regarding diabetes (27% *vs.* 42%, $p = 0.39$), BMI (28.9 ± 6.6 kg/m^2 *vs.* 27.2 ± 4.2 kg/m^2, $p = 0.55$), or other comorbidities known as HFpEF risk factors (hypertension, metabolic syndrome, history of ischemic cardiomyopathy, sleep apnea syndrome).

In multivariable logistic regression, NT-proBNP, H_2FPEF score, EAT, and hemoglobin were independent associated factors of HFpEF (Fig. 2B, Table S3 in Additional file 1). Using random forest statistical analysis, we found that the best markers of HFpEF status were NT-proBNP, EAT, indexed LA volume, H_2FPEF score, and

Table 1 Baseline characteristics of controls, pre-HF patients, and HFpEF patients in the Belgian cohort, matched for age and sex

	Control	Pre-HF stage B	HFpEF stage C	P-value
	N = 26	N = 16	N = 104	
Baseline characteristics				
Age (years)	76 ± 5	75 ± 4	77 ± 8	0.616
Female (n, %)	17 (65.4%)	10 (62.5%)	58 (55.8%)	0.629
BMI (kg/m^2)	25.5 ± 3.3	27.2 ± 4.2	28.9 ± 6.6*	0.028
Heart rate (beat/min)	66.4 ± 8.8	66.2 ± 8.8	71.5 ± 14.1	0.105
Systolic blood pressure (mmHg)	144 ± 21.8	156 ± 17.5	138 ± 21.8*	0.005
Diastolic blood pressure (mmHg)	80.4 ± 12.5	79.1 ± 13.6	75.1 ± 13.1	0.133
NYHA class III and IV (n, %)	0 (0%)	0 (0%)	43 (41.3%)*#	< 0.001
H_2FPEF score	2.2 ± 1.0	4.3 ± 1.4$^{\nabla}$	6.0 ± 1.8*#	< 0.001
Obesity	2 (7.7%)	5 (31.2) $^{\nabla}$	37 (35.6)*	0.022
Metabolic syndrome	2 (7.7%)	1 (9.1%)	10 (11.2%)	0.891
Medical history				
Atrial fibrillation (n, %)	1 (3.9%)	3 (18.8%)	62 (59.6%)*#	< 0.001
Ischemic cardiomyopathy (n, %)	0 (0%)	5 (31.2%)$^{\nabla}$	38 (36.5%)*	0.002
COPD (n, %)	0 (0%)	0 (0%)	11 (10.6%)	0.092
Sleep apnea (n, %)	0 (0%)	1 (6.3%)	12 (11.8%)	0.152
Cardiovascular risk factors				
Hypertension (n, %)	17 (65.4%)	14 (93.3%)	96 (92.3%)*	0.001
Diabetes (n, %)	3 (11.5%)	4 (26.7%)	44 (42.3%)*	0.010
Hypercholesterolemia (n, %)	23 (88.5%)	12 (80.0%)	71 (68.9%)	0.096
Smoking (n, %)	5 (19.2%)	5 (33.3%)	43 (41.7%)	0.100
Family history of CV disease (n, %)	3 (11.5%)	5 (33.3%)	19 (18.4%)	0.052
Medication				
ACE inhibitor—ARBs (n, %)	10 (38.5%)	11 (73.3%)	70 (67.3%)*	0.017
Beta blocker (n, %)	3 (11.5%)	9 (60.0%)$^{\nabla}$	70 (67.3%)*	< 0.001
Loop diuretics (n, %)	0 (0%)	2 (13.3%)	72 (69.9%)*#	< 0.001
Thiazide (n, %)	2 (7.7%)	6 (40.0%)	22 (21.4%)	0.054
MRA (n, %)	0 (0%)	1 (6.7%)	20 (19.2%)	0.029
Anticoagulants (n, %)	1 (3.9%)	3 (20.0%)	54 (51.9%)*	< 0.001
Antiplatelet agents (n, %)	5 (19.2%)	6 (40.0%)	45 (43.3%)	0.079
Statins (n, %)	7 (26.9%)	8 (53.3%)	51 (49.0%)	0.105
Echocardiography study				
LA diameter (mm)	32.8 ± 4.9	40.9 ± 7.5$^{\nabla}$	45.6 ± 7.0*#	< 0.001
LA volume, indexed (ml/m^2)	19.0 ± 5.9	30.7 ± 10.4$^{\nabla}$	44.2 ± 19.1*#	< 0.001
LV EDV, indexed (mL/m^2)	60.6 ± 9.7	56.0 ± 10.8	66.2 ± 17.2#	< 0.001
LV ESV, indexed (mL/m^2)	21.5 ± 5.9	18.9 ± 5.5	25.3 ± 9.9#	< 0.001
LV ejection Fraction (%)	64.9 ± 5.3	66.6 ± 5.6	62.6 ± 7.2	0.024
LV global longitudinal strain (%)	− 20.9 ± 2.6	− 18.8 ± 2.4	− 16.6 ± 3.1*#	0.011
E/A ratio	0.7 ± 0.1	1.4 ± 0.9$^{\nabla}$	1.3 ± 0.8*	0.045
E/e' septal ratio	9.7 ± 1.8	17.1 ± 5.4$^{\nabla}$	17.7 ± 6.9*	< 0.001
E deceleration time (ms)	196 ± 37.7	158 ± 39.9	163 ± 57.5*	0.002
eSPAP (mmHg)	18.0 ± 5.3	31.1 ± 14.5	31.1 ± 9.7*	< 0.001
RA volume, indexed (ml/m^2)	17.7 ± 4.9	28.1 ± 13.0	34.6 ± 18.6*	< 0.001
RV fractional area change (%)	47 ± 7	46 ± 7	42 ± 9*	0.005
TAPSE (mm)	23.9 ± 3.6	23.7 ± 4.8	19.0 ± 5.3*#	0.009
RV global longitudinal strain (%)	− 27.9 ± 4.2	− 26.6 ± 3.7	− 23.4 ± 4.4*	< 0.001
Venous cava diameter (mm)	11.6 ± 3.9	12.1 ± 4.9	15.4 ± 7.0*	0.011
CMR study				
EAT, ventricular, diastolic, indexed (ml/m^2)	48.0 ± 8.9	55.0 ± 11.8	72.4 ± 20.8*#	< 0.001
EAT, ventricular, systolic, indexed (ml/m^2)	48.4 ± 10.1	58.9 ± 12.8	73.1 ± 20.9*#	< 0.001
LA volume, indexed (mL/m^2)	31.5 ± 9.29	52.5 ± 16.6$^{\nabla}$	66.4 ± 30.3*	< 0.001
LV mass, indexed (g/m^2)	59.1 ± 12.1	58.8 ± 12.1	67.7 ± 15.4*	0.006

Table 1 (continued)

	Control	Pre-HF stage B	HFpEF stage C	P-value
	N = 26	N = 16	N = 104	
LV EDV, indexed (mL/m^2)	64.5 ± 11.7	65.5 ± 12.9	73.7 ± 18.9*	0.022
LV ESV, indexed (mL/m^2)	22.5 ± 7.1	20.8 ± 5.4	28.3 ± 11.5*#	0.003
LV ejection fraction (%)	65.6 ± 6.1	68.2 ± 5.7	62.5 ± 8.2#	0.008
RV ejection fraction (%)	61.0 ± 6.4	62.6 ± 8.5	57.0 ± 7.7*#	0.004
LGE (%)	0.0 ± 0.0	0.6 ± 1.2	1.5 ± 2.7*#	0.009
ECV (%)	27.9 ± 2.4	28.3 ± 3.5	32.4 ± 4.6*#	< 0.001
Biology				
NT-proBNP (pg/mL)	106 [56.6–143]	422 [364–686] ∇	1850 [829–3336]*#	< 0.001
eGFR (mL/min/1.73m^2) by CK-EPI	71.0 [54.5–80.8]	57.0 [49.5–68.5]	55.0 [40.8–67.0]*	0.004
Hemoglobin (g/dL)	13.8 [12.8–14.5]	13.2 [12.2–14.2]	11.6 [10.5–12.9] *#	< 0.001
Blood glucose (mg/dL)	93.5 [87.8–100]	98.5 [94.2–111]	108 [94.0–143]*	0.002
Total cholesterol (mg/dL)	205 [184–227]	178 [142–224]	146 [122–172]#	< 0.001
LDL-C (mg/dL)	118 [98.8–142]	104 [70.0–128]	70.0 [50.5–94.0]*#	< 0.001
HDL-C (mg/dL)	66.5 [58.8–78.5]	48.0 [44.5–57.8] ∇	51.0 [40.0–60.8]*	< 0.001
Triglycerides (mg/dL)	98.5 [75.8–124]	118 [102–184]	90.0 [71.0–122]#	0.048
TyG index	4.6 ± 0.2	4.9 ± 0.3∇	4.7 ± 0.3	0.04
CRP (mg/dL)	0.20 [0.10–0.20]	0.20 [0.10–0.80]	0.70 [0.20–2.28]*	< 0.001
hsTnT (pg/mL)	7.0 [6.0–11.0]	12.0 [5.0–15.0]	24.0 [14.0–33.2]*#	< 0.001
FGF-23 (RU/mL)	62.2 [55.6–74.1]	75.3 [63.4–105]	211.0 [116.0–489.0]*#	< 0.001
Soluble ST2 (ng/mL)	24.6 [20.7–31.9]	24.5 [22.8–34.0]	39.1 [28.6–55.2]*#	< 0.001
Leucocytes (10^3/µL)	6.20 [5.4–7.7]	7.73 [5.9–8.3]	7.4 [6.0–9.4]*	0.136
Neutrophils (10^3/µL)	3.6 [3.2–4.6]	5.04 [3.7–5.9]	4.8 [3.9–6.3]	0.012
Lymphocytes (10^3/µL)	1.7 [1.5–2.2]	1.3 [1.2–1.7]	1.4 [1.0–1.8]	0.051
Monocytes (10^3/µL)	0.6 [0.4–0.7]	0.7 [0.6–0.8]	0.7 [0.6–0.9]*	0.024
NLR	2.1 [2.0–2.6]	3.4 [2.4–4.7]	3.1 [2.4–5.0]*	0.001

ACE Angiotensin-converting enzyme, *BMI* Body mass index, *CK-EPI* Chronic Kidney Disease Epidemiology Collaboration, *CMR* Cardiovascular magnetic resonance, *COPD* Chronic obstructive pulmonary disease, *CRP* C-reactive protein, *CV* Cardiovascular, *ECV* Extracellular volume, *EDV* End-diastolic volume, *ESV* End-systolic volume, *eGFR* Estimated glomerular filtration rate, *eSPAP* Estimated systolic pulmonary artery pressures, *FGF-23* Fibroblast growth factor 23, *HF* Heart failure, *HFpEF* Heart failure with preserved ejection fraction, *HDL-C* High-density lipoprotein cholesterol, *hsTnT* High-sensitive troponin T, *LA* Left atrium, *LGE* Late gadolinium enhancement, *LDL-C* Low-density lipoprotein cholesterol, *LV* Left ventricular, *MPV* Mean platelet volume, *MRA* Mineralocorticoid receptor antagonist, *NT-proBNP* N-terminal pro B-type natriuretic peptide, *NLR* Neutrophil-to-lymphocyte ratio, *NYHA* New York Heart Association, *SBP* Systolic blood pressure, *TAPSE* Tricuspid annular plane systolic excursion, *ST2* Suppression of tumorigenicity-2

Metabolic score was calculated using the following criteria: hypertension, obesity (BMI ≥ 30 kg/m^2), hypercholesterolemia according to sex, hypertriglyceridemia, hyperglycemia. Metabolic syndrome was defined as a metabolic score > 3

Values are mean ± standard deviation or median and interquartile range (IQR 0.25–0.75). Categorical variables are expressed as counts and proportions. Differences between clinical characteristics were compared using ANOVA with Tukey's post-hoc analysis or Chi-square test, as appropriate

*P-value < 0.05 control compared to HFpEF

#P-value < 0.05 pre-HF compared to HFpEF

∇P-value < 0.05 pre-HF compared to control

hemoglobin (Fig. 2C, Table S4 in Additional file 1). Interestingly, both statistical approaches identified EAT as a robust parameter associated with HFpEF stage. Of note, diabetes was not markers of the transition to symptomatic HFpEF. Despite a significant correlation between BMI and EAT, multivariable analysis (Table S5 in Additional file 1) showed that BMI was not independently associated with HFpEF, while EAT remained significant, with no evidence of collinearity (VIF < 4).

Baseline characteristics and EAT volume comparison between the Belgian and Beta3-LVH cohorts

Baseline characteristics of the pre-HF patients of the Beta3-LVH cohort are summarized in Table S6. Compared to the Beta3-LVH cohort, the Belgian cohort consisted of older pre-HF and HFpEF patients, with a higher prevalence of diabetes, higher H_2FPEF scores, more patients with AF and low eGFR (Table 2). Structurally, only diastolic function was more impaired in the Belgian group, as reflected by higher E/e' ratios. Indexed EAT volume was similar in the pre-HF group from the Belgian and the Beta3-LVH (55.0 ± 11.8 ml/m^2*vs.* 52.0 ± 15.0 ml/m^2, p = 0.91), but significantly higher in the HFpEF group from the Belgian cohort (Fig. 1, Table 2). The difference in indexed EAT volume between the HFpEF and pre-HF groups (combining the Belgian and Beta3-LVH cohorts) remains significant even after adjusting for age, sex, and cohort effects (p < 0.001).

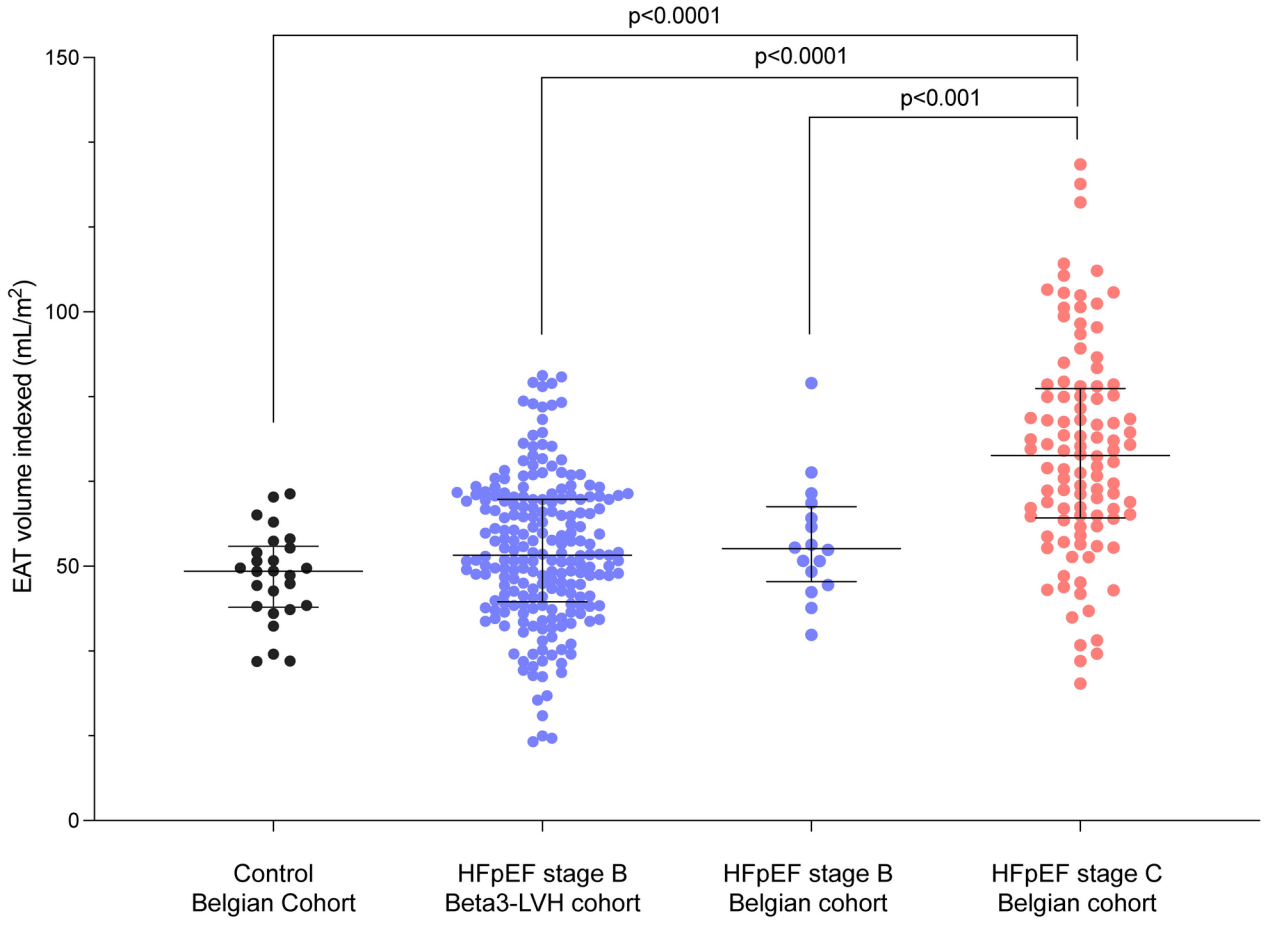


Fig. 1 Boxplot, indexed EAT volume of controls, pre-HF (stage B) patients, and HFpEF (stage C) patients in the Belgian and Beta3-LVH cohorts. Comparison by ANOVA and Dunnett's post-hoc analysis

Association of EAT with HFpEF status in the Belgian and Beta3-LVH cohort

In the univariable analysis, indexed EAT volume was significantly associated with HFpEF status, along with age, female sex, diabetes, eGFR, E/e' ratio, AF, and the H_2FPEF score. In the multivariable analysis, we simplified the model by retaining only the H_2FPEF score, as it includes key variables such as AF, sex, and E/e' ratio. The analysis confirmed that EAT remained a significant and independent factor associated with the HFpEF status. Notably, there was no significant interaction between cohort and EAT volume indexed ($p = 0.99$), indicating that the effect of EAT is consistent across cohorts (Table S7 in Additional file 1).

Markers associated with increased EAT in controls, pre-HF and HFpEF patients in the Belgian cohort

Next, we aimed to identify the clinical, biological, and imaging parameters correlated with the increase in indexed EAT volume in the overall Belgian cohort illustrated by Fig. 3 and Table 3. Increased EAT was significantly correlated with BMI, H_2FPEF score, blood glucose, NT-proBNP, hsTnT, cFGF-23, and lower eGFR. Interestingly, neutrophils, CRP, and sST2 were also positively correlated with EAT, suggesting a link to inflammation. Regarding imaging markers, EAT was positively correlated with atrial volume on echocardiography, E/e' ratio, indexed LV mass on CMR, and LGE, while it was negatively correlated with TAPSE and LV GLS.

Profile of HFpEF patients with elevated EAT in the Belgian cohort

To gain deeper insight into the role of elevated EAT in HFpEF patients, we examined patient characteristics by categorizing them based on their indexed EAT volume, above or below the median (71.7 ml/m^2), as presented in Table S8. Patients with higher EAT were younger, had more frequent diabetes and history of ischemic cardiomyopathy, and had more metabolic disorders. They exhibited lower eGFR and higher levels of neutrophils, sST2, and hsTnT. They also had pronounced diastolic dysfunction (with higher E/A ratio, E/e ratio', LA diameter) and focal fibrosis (with higher LGE). Of note, systolic function was also impaired with lower LV GLS and

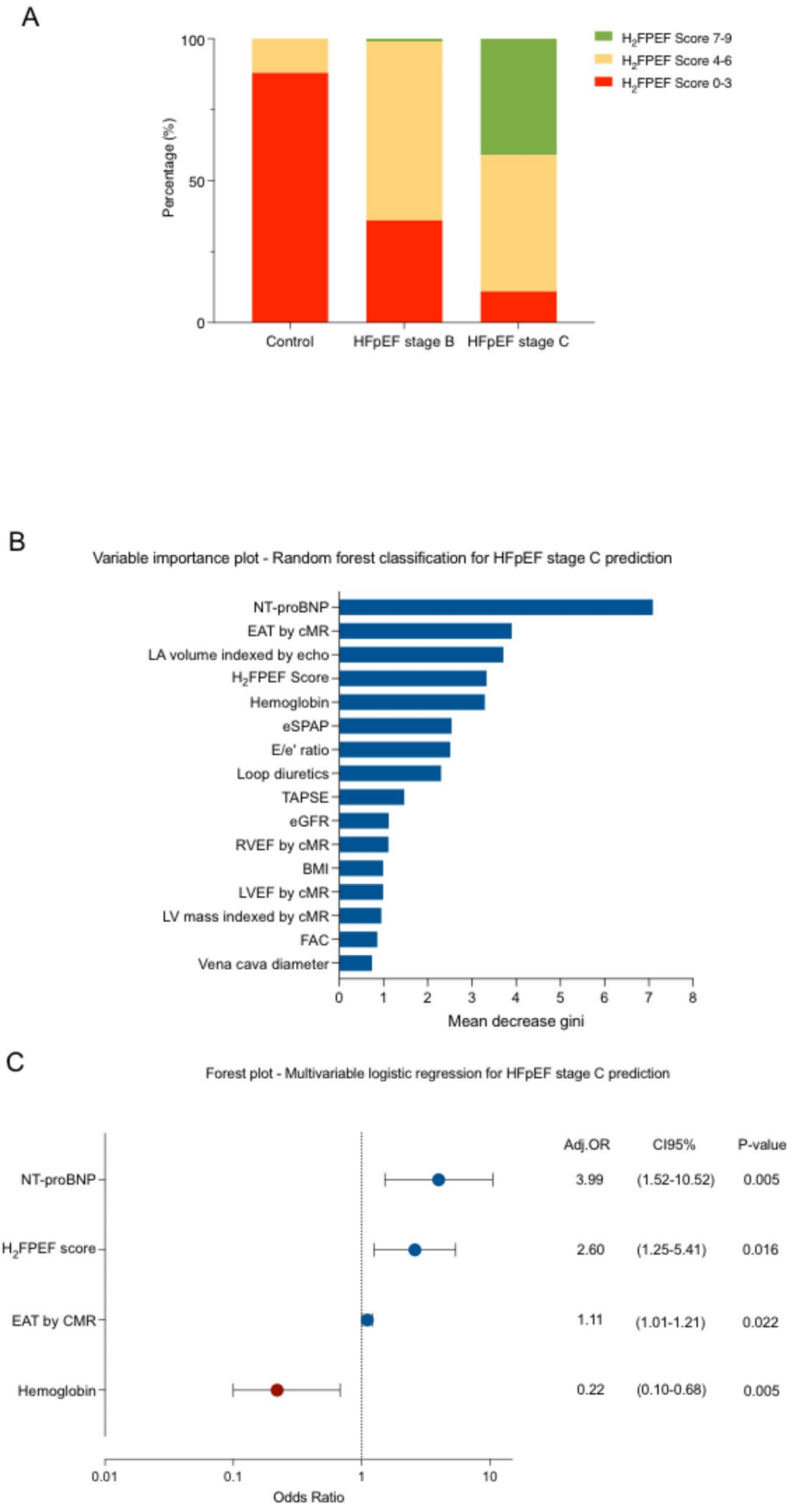


Fig. 2 Distribution of H_2FPEF score category within control, pre-HF, and HFpEF patients **A** in the Belgian cohort; Associated factors of HFpEF illustrated by multivariable logistic regression analysis **B** and random forest classification analysis **C** in the Belgian cohort. *EAT* Epicardial adipose tissue, *HF* Heart failure, *HFpEF* Heart failure with preserved ejection fraction

Table 2 Baseline characteristics of controls, pre-HF patients, and HFpEF patients in the Belgian and the Beta3-LVH cohorts

	Belgian cohort	Beta3-LVH cohort	Belgian cohort	Belgian cohort
	Controls	Pre-HF	Pre-HF	HFpEF
	N = 26	N = 191	N = 16	N = 104
Age (years)	76 ± 5	64 ± 10	75 ± 4	77 ± 8
Female (n, %)	17 (65.4%)	53 (27.7%)	10 (62.5%)	58 (55.8%)
BMI (kg/m^2)	25.5 ± 3.3	29.8 ± 4.41	27.2 ± 4.2	28.9 ± 6.6
Diabetes (n, %)	3 (11.5%)	37 (19.4%)	4 (26.7%)	44 (42.3%)
Atrial fibrillation (n, %)	1 (3.9%)	3 (1.6%)	3 (18.8%)	62 (59.6%)
eGFR (mL/min/1.73m^2) by CK-EPI	71.0 [54.5–80.8]	78.2 [69.9–91.0]	57.0 [49.5–68.5]	55.0 [40.8–67.0]
LA volume indexed (ml/m2) by Echo	19.0 ± 5.9	34.0 ± 11.0	30.7 ± 10.4	44.2 ± 19.1
LV ejection Fraction (%) by Echo	64.9 ± 5.3	63.0 ± 6.0	66.6 ± 5.6	62.6 ± 7.2
LV mass indexed (g/m^2) by CMR	59.1 ± 12.1	58.0 ± 7.0	58.8 ± 12.1	67.7 ± 15.4
E/e' ratio	9.7 ± 1.8	9.3 ± 3.1	17.1 ± 5.4	17.7 ± 6.9
H_2FPEF Score	2.2 ± 1.0	3.1 ± 1.4	4.3 ± 1.4	6.0 ± 1.8
Indexed EAT volume (ml/m^2)	48.0 ± 8.9	52.0 ± 15.0	55.0 ± 11.8	72.4 ± 20.8

BMI Body mass index, *CMR* Cardiac magnetic resonance, *EAT* Epicardial adipose tissue, *eGFR* Estimated glomerular filtration rate, *HF* Heart failure, *HFpEF* Heart failure with preserved ejection fraction, *LV* Left ventricular

LVEF. However, percentage of NYHA class III or IV, NT-proBNP levels, and diuretic use were similar in the two groups.

In univariable linear regression analysis, diabetes, BMI, metabolic syndrome, history of ischemic cardiomyopathy, impaired LV GLS, elevated E/e' ratio, higher neutrophil count, and increased levels of hsTnT and sST2 were all found to be associated with elevated EAT in HFpEF patients (Table 4). Of note, antidiabetic medications in diabetic patients were not associated with EAT volume.

In multivariable linear regression analysis, only diabetes (β: 8.32 [0.15–16.49], p = 0.046), history of ischemic cardiomyopathy (β: 10.76 [2.58–18.94], p = 0.011), and sST2 (β: 21.18 [2.39–39.97], p = 0.028) were independently associated with increased EAT..

EAT and clinical outcomes in HFpEF in the Belgian cohort

Over a median follow-up of 51 months [31–65 months], 42 patients (40%) died, and 56 patients (54%) were hospitalized for HF. Overall, 68 patients (65%) reached the composite endpoint of all-cause mortality or HF hospitalization, whichever came first. Kaplan-Meier curves for the composite endpoint according to median indexed EAT volume (< 71.7 ml/m^2 and ≥ 71.7 ml/m^2) showed that patients with elevated indexed EAT volume did not have worse prognosis (Figure S3). In contrast, diabetes and low BMI were associated with poor clinical outcome (Fig. 4).

Table 3 Correlation between biventricular indexed EAT volume and clinical, imaging, biological continuous variables in controls, pre-HF patients, and HFpEF patients in the Belgian cohort, matched for sex and age

Variables	R Pearson	P-value
Age	− 0.05	0.54
BMI	0.30	< 0.001
NT-proBNP	0.37	< 0.001
eGFR by CK-EPI	− 0.21	0.013
Triglycerides	− 0.05	0.60
Blood glucose	0.22	0.011
hsTnT	0.41	< 0.001
FGF-23	0.22	0.009
Soluble ST2	0.30	< 0.001
Neutrophils	0.26	0.002
CRP	0.22	0.016
H_2FPEF score	0.41	0.003
LA volume, indexed, by echo	0.33	< 0.001
RA volume, indexed, by echo	0.19	0.025
EF Simpson by echo	− 0.14	0.08
E/e'	0.33	< 0.001
TAPSE	− 0.33	< 0.001
LV global longitudinal strain	0.35	< 0.001
RV global longitudinal strain	0.19	0.09
LV mass, indexed, by cMR	0.20	0.015
ECV	0.14	0.095
LGE	0.24	0.004

BMI Body mass index, *CK-EPI* Chronic Kidney Disease Epidemiology Collaboration, *CMR* Cardiovascular magnetic resonance, *CRP* C-reactive protein, *ECV* Extracellular volume, *eGFR* Estimated glomerular filtration rate, *FGF-23* Fibroblast growth factor-23, *HF* Heart failure, *hsTnT* High-sensitive troponin T, *LA* Left atrium, *LGE* Late gadolinium enhancement, *LV* Left ventricular, *NT-proBNP* N-terminal pro B-type natriuretic peptide, *TAPSE* Tricuspid annular plane systolic excursion, *ST2* Suppression of tumorigenicity-2

We analyzed the prognostic impact of EAT in specific subgroups, including diabetic and non-metabolic HFpEF patients. In both subgroups, EAT was not significantly associated with prognosis, confirming the consistency of our findings across different phenotypes of HFpEF (Figure S4–S5 in Additional file 1).

EAT and HFpEF patients with diabetes in the Belgian cohort

As diabetes is a key marker associated with elevated EAT and a prognostic factor in HFpEF, we examined its impact on patient characteristics. HFpEF patients with diabetes (42%) had a distinct profile compared to those without diabetes. They were generally younger, with a higher prevalence of metabolic syndrome and a history of ischemic cardiomyopathy. These patients also had an elevated E/e' ratio, increased LV mass index, more significant LGE, lower eGFR, and higher TyG index and hsTnT levels. Notably, they had significantly higher indexed EAT volume compared to non-diabetic HF patients (80.8 ± 21.9 *vs.* 66.3 ± 17.7 ml/m^2, p < 0.001) (Fig. 5, Table S9 in Additional file 1). Additionally, indexed EAT

Table 4 Associated factors of biventricular indexed EAT volume in multivariable linear regression analysis in HFpEF patients in the Belgian cohort

	Univariable analysis			Multivariable analysis		
Variables	**Beta**	**95% CI**	**P-value**	**Beta**	**95% CI**	**P-value**
Age (years)	− 0.26	− 0.78, 0.27	0.33			
Diabetes	14	6.80, 22	< 0.001	8.32	0.15, 16.49	0.046
Female	− 1.8	− 10.0, 6.40	0.66			
BMI (kg/m^2)	0.75	0.15, 1.40	0.015			
Metabolic syndrome	13	− 0.43, 26	0.058			
Atrial fibrillation history	0.33	− 7.90, 8.60	0.94			
Ischemic cardiomyopathy history	13	5.20, 21	0.0010	10.76	2.58, 18.94	0.011
Hypercholesterolemia	3.70	− 5.10, 13	0.41			
Ejection fraction, Simpson (%), by echo	− 0.22	− 0.79, 0.34	0.44			
LV global longitudinal strain (%)	1.40	0.13, 2.70	0.032	0.86	-0.38, 2.11	0.17
RV fractional area change	− 6.90	− 55, − 41	0.80			
E/e' ratio	0.70	0.13, 1.30	0.016			
Left ventricle mass, indexed, by CMR (g/m^2)	0.20	− 0.07, 0.46	0.14			
LGE (%)	1.20	− 0.34, 2.70	0.13			
eGFR by CK-EPI (ml/min/1.73m^2)	− 0.12	− 0.32, 0.09	0.26			
Blood glucose (mg/dL)	0.05	− 0.02, 0.12	0.13			
Glycated hemoglobin (log %)*	− 0.72	− 5.40, 4	0.76			
Triglycerides (mg/dL)	0.01	− 0.08, 0.11	0.77			
CRP (log mg/dL)	1.10	− 5.40, 7.60	0.74			
Neutrophils (log 10^3/µL)	23	0.75, 46	0.043			
hsTnT (log pg/mL)	12	− 1.50, 26	0.080			
NT-proBNP (log pg/mL)	1.10	− 8.10, 10	0.81			
FGF-23 (log RU/mL)	− 0.94	− 9.80, 7.90	0.83			
ST2 soluble (log ng/mL)	16	− 2.70, 35	0.092	21.18	2.39,39.97	0.028
Mean platelet volume (fL)	− 3.40	− 7.70, 0.80	0.11			
Insulin*	− 1.9	− 15, 12	0.78			
Gliptin*	− 1.8	− 25, 22	0.88			
Metformin*	− 3.3	− 21, 14	0.71			

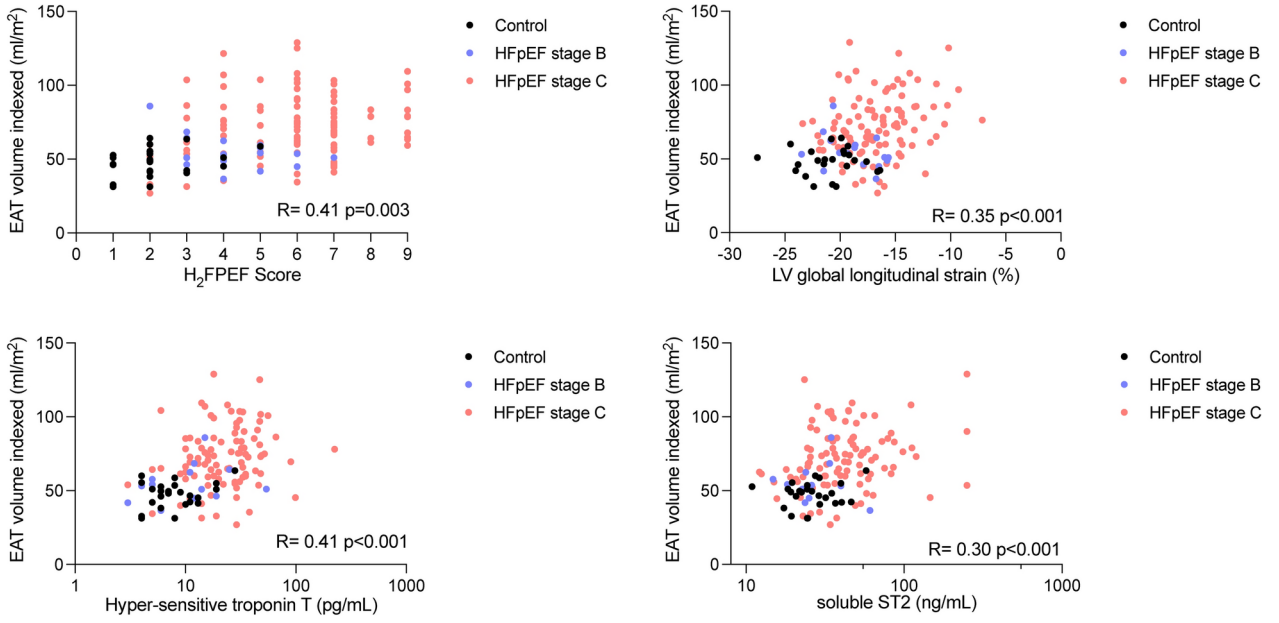


Fig. 3 Scatter plot of H_2FPEF score, LV global longitudinal strain, high-sensitive troponin T, soluble ST2, and indexed EAT volume in the Belgian cohort. *EAT* Epicardial adipose tissue, *LV* Left ventricular

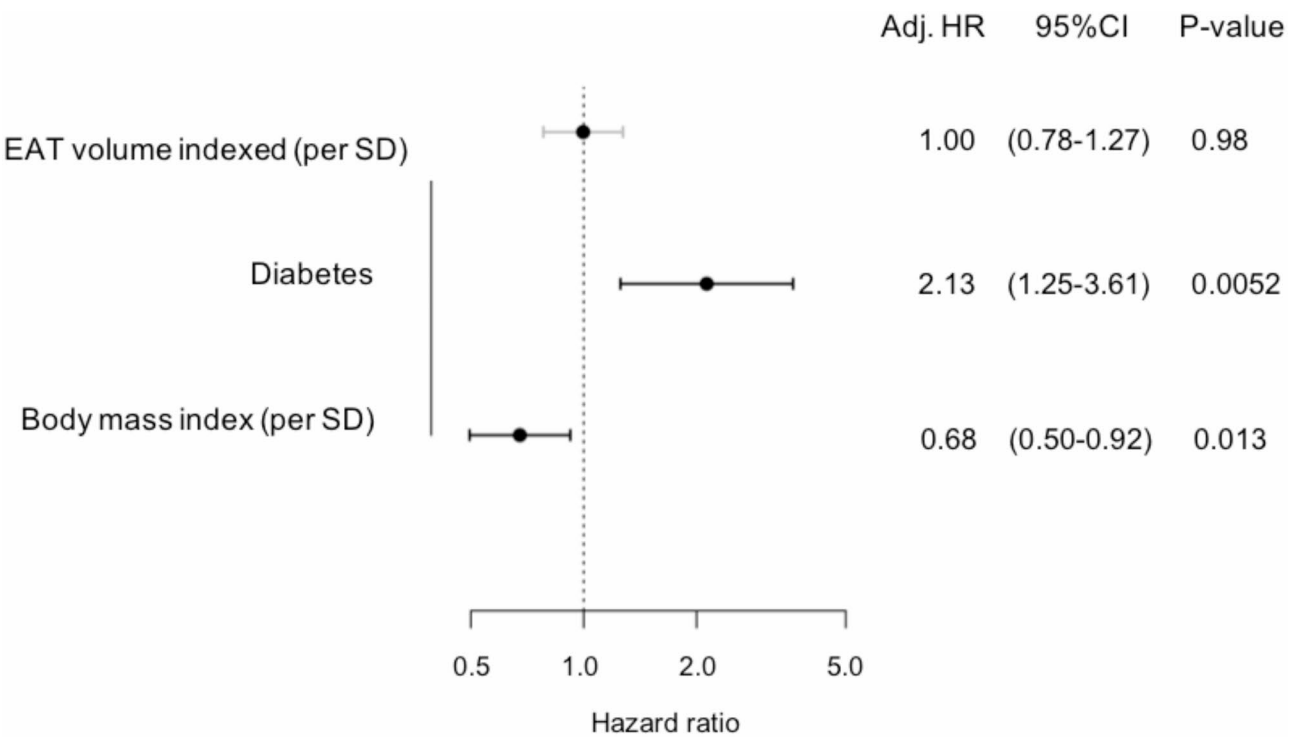


Fig. 4 Forest plot, multivariable Cox regression analysis of all-causes mortality and heart failure hospitalization in the Belgian cohort

volume was positively correlated with metabolic scores, with a greater proportion of diabetics in the higher range.

Discussion

Summarized findings

In the present study, we were able to demonstrate a difference between controls, pre-HF patients (stage B), and HFpEF patients (stage C) with respect to EAT volume, which appears to increase throughout the pathophysiological pathway. No study had previously assessed EAT volume between pre-HF and HFpEF stages. Pre-HF patients did not have higher EAT volume compared to controls. Although the phenotype did not differ substantially from pre-HF patients in terms of diabetes prevalence and BMI, HFpEF patients had significantly higher EAT volume, higher LA volume with more AF, and an inflammatory milieu. We confirmed the distinction between pre-HF and HFpEF patients with the Beta3-LVH cohort. Moreover, among HFpEF patients from the Belgian cohort, those with higher EAT were characterized by diabetes, history of ischemic cardiomyopathy, metabolic disorders, and inflammatory state. Finally, EAT was not a prognostic marker in HFpEF patients. Overall, our results are consistent with previous studies showing a strong association between EAT, inflammation, metabolic comorbidities, and HFpEF, but for the first time bring interesting data regarding pre-HF patients. Altogether, our findings support that EAT may be a major contributor to the pathogenesis of HFpEF.

EAT and HF stages

EAT is an established indicator of overweight (BMI > 25 kg/m^2), obesity (BMI > 30 kg/m^2), and T2DM in the HFpEF population [21]. Moreover, a comprehensive analysis of a large cohort has shown that increased EAT volume correlates with increased levels of VAT and overall adipose tissue, as well as an increased risk of HF, even after adjustment for BMI. Numerous studies have now shown that EAT volume is increased in HFpEF patients, regardless of BMI [5]. Consequently, obesity and diabetes could theoretically contribute to an increase in EAT and the onset of HF [9]. Indeed, insulin resistance is closely linked to the expansion of EAT, which is associated with fat accumulation and myocardial lipotoxicity [22]. Nevertheless, our data showed that elevated BMI and prevalence of diabetes were not the distinguishing factors between pre-HF and HF patients, even though these two groups have disparate EAT levels with comparable cardiac structural alterations. However, based on our study, we cannot exclude the possibility that a subset of our pre-HF patients may still progress to a symptomatic stage. The abnormal increase and dysfunction of EAT likely play a role in cardiac remodeling, leading to atrial dilatation, occurrence of AF, and therefore onset of symptoms [23]. Furthermore, AF carries significant weight in the H_2FPEF score, accounting for one-third of the points. H_2FPEF correlated well with increased EAT and was also an independent associated factor of HFpEF status.

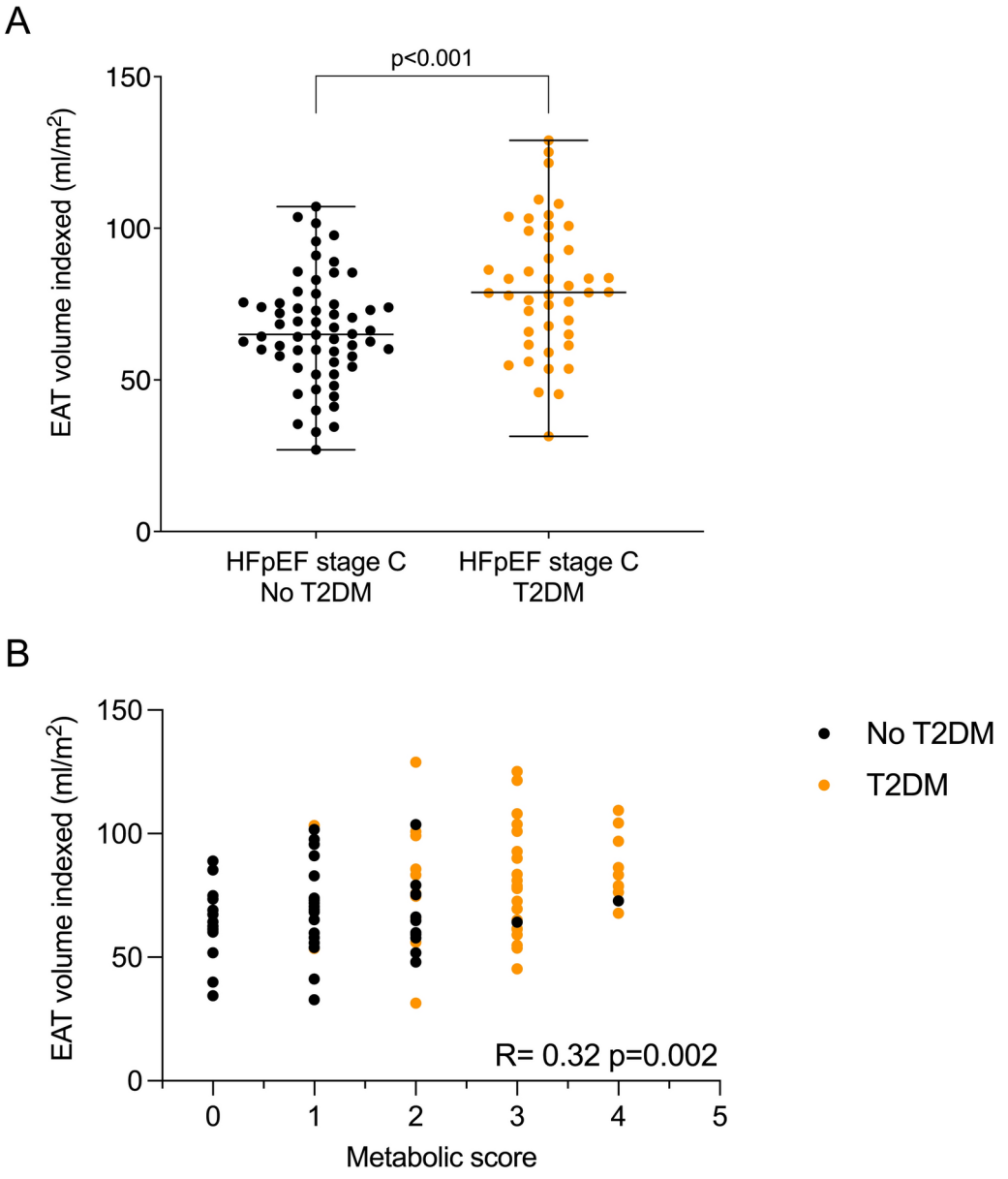


Fig. 5 Boxplot, EAT volume of non-diabetic and diabetic HFpEF patients in the Belgian cohort **A** Scatter plot of metabolic score and indexed EAT volume **B** in the Belgian cohort

Thus, EAT may be a determinant of HFpEF in certain patients, but this phenomenon cannot be attributed to metabolic factors alone. It probably involves metabolic and/or genetic factors, as well as aging and advanced chronic disease, which have been shown to influence and affect the genetic profile and function of EAT [24, 25]. To address this uncertainty, longitudinal studies that follow patients throughout their progression to HFpEF may provide valuable insights into whether the increase in EAT precedes or accompanies inflammation. The role of EAT in HFpEF—whether it is an active contributor or an innocent bystander—is still uncertain [6].

EAT and cardiometabolic factors in HFpEF patients

Diabetes, ischemic cardiomyopathy, and sST2 were independent markers of elevated EAT, highlighting a cardiometabolic profile in symptomatic HFpEF patients. A meta-analysis of several studies suggests that diabetic individuals have significantly higher levels of EAT than healthy controls, regardless of the type of diabetes (type 1 diabetes mellitus or T2DM), BMI, and EAT measurement technique used [26]. Under physiological conditions, EAT exhibits characteristics of both white and brown fat and has cardioprotective functions such as free fatty acid supply and thermoregulation of the adjacent myocardium [5]. Diabetes and obesity contribute to the increase

in white fat and EAT adipocytes release large amounts of free fatty acids, triggering macrophage infiltration and secretion of pro-inflammatory cytokines while reducing adiponectin production [27]. These changes may affect nearby cardiac muscle, as shown in a study where rat cardiomyocytes incubated with EAT biopsy media from diabetic patients became dysfunctional and insulin resistant. In addition, EAT secretory products in diabetic patients have been shown to impair cardiomyocyte contractile function and free fatty acid oxidation [28].

Our study highlights the association between EAT and coronary artery disease in HFpEF patients. The literature also shows a strong association between EAT and coronary artery disease, with pro-inflammatory characteristics in those with cardiovascular risk factors or existing disease, as well as an association with coronary microvascular dysfunction [17]. EAT induces the production and accumulation of several pro-inflammatory adipokines, including interleukin (IL)-6, tumor necrosis factor-α, monocyte chemotactic protein-1, and leptin, thereby increasing local inflammation and affecting both the heart and coronary arteries [29]. In addition, our results suggest several hypotheses regarding the complex role of diabetes in either the development of coronary artery disease or the increase in EAT. EAT dysfunction, seen in both obesity and diabetes, increases lipolysis and may accelerate coronary atherosclerosis and cardiomyocyte lipotoxicity [30].

Our study found significantly higher levels of inflammatory markers associated with increased EAT, consistent with the concept of metainflammation—metabolically induced inflammation—that has gained recognition in the pathogenesis of HFpEF [1]. Chronic inflammation plays a role in the expansion and dysfunction of EAT, while conversely, the expansion and dysfunction of EAT itself can become a driving force of inflammation [31].

Several studies confirm that EAT has a more pro-inflammatory profile than intra-abdominal VAT, contributing to both local and systemic low-grade inflammation in HFpEF [32, 33]. Notably, sST2, which was strongly associated with EAT and HFpEF in our study, is an inflammatory marker and pro-fibrotic cardiac agent. By competing with IL-33 for the ST2 receptor, sST2 disrupts the cardioprotective ST2/IL-33 pathway that normally limits cardiac fibrosis and hypertrophy [34]. Dysfunctional EAT has been identified as one of the sources of sST2 production [35]. Although sodium/glucose cotransporter 2 (SGLT2) inhibitors—the only validated treatment for HFpEF—are known to reduce both EAT and the pro-inflammatory state, one study did not show a reduction in sST2 levels [36].

Clinical and therapeutic perspectives

Our findings open the discussion on several clinical perspectives. HFpEF patients differ from pre-HF patients primarily by a significant increase in EAT, which leads to cardiac remodeling through inflammation and a pericardial restraint effect. This remodeling is mainly characterized by myocardial fibrosis and increased atrial dilatation, which can lead to AF and consequently symptom onset. Therefore, it seems important to act and prevent the increase of EAT in all patients with metabolic risk factors.

Several treatments have demonstrated an effect on EAT volume and function in non-HFpEF subjects. Among them, SGLT2 inhibitors are associated with a lower incidence of AF, possibly due to reduced EAT, and with a diuretic effect that reduces plasma volume and promotes ventricular mass regression, which may decrease the pericardial restraint effect [37–39]. GLP-1 receptor agonists (GLP-1 RA) reduce EAT thickness and promote myocardial remodeling in diabetic and obese patients [40].

In HFpEF patients, our results reveal that increased EAT is mainly associated with diabetes, highlighting the important role of antidiabetic drugs, which are known to reduce EAT levels and impact prognosis. SGLT2 inhibitors are the first agents shown to improve quality of life and reduce HF hospitalizations in HFpEF [41, 42]. A recent study showed that GLP-1 RAs improve quality of life in obese HFpEF patients and have additional benefits such as weight loss and cardiovascular protection [43]. However, the impact of SGLT2 inhibitors and GLP-1 RAs on EAT volume and activity and their association with improved HFpEF outcomes remain unclear. Further studies are needed to clarify these relationships.

EAT and clinical prognosis

Although numerous studies have found an association between increased EAT and poor prognosis in HFpEF, we did not confirm these findings [8, 44]. However, a meta-analysis on EAT in HF found no significant association between EAT and an increased risk for the composite outcome of cardiovascular death and hospitalization for HF in HFpEF patients [45]. Another study revealed that EAT volume in HFpEF patients was not associated with prognosis [46]. Our result may be explained either by the "obesity paradox", where obese HFpEF patients tend to have a better prognosis than non-obese patients. In our study, BMI was positively correlated with increased EAT volume, which may partially illustrate the lack of association between increased EAT volume and clinical outcome [47]. Thus, we should pay attention to the prognostic role of EAT volume if it is itself influenced by obesity that has a protective effect and diabetes that plays a prognostic role.

Limitations

Our study has several limitations. Although the Beta3-LVH cohort served as a confirmation cohort, it was distinctly different from the Belgian cohort, with less cardiac remodeling, and overall, less advanced disease. Despite these differences, the marked distinction in EAT between pre-HF and HFpEF remained significant, further highlighting the critical role of EAT in disease progression. This strengthens the relevance of EAT as a contributing factor in the onset of HFpEF, beyond cohort-specific variations. In addition, the lack of additional metabolic parameters, such as the homeostasis model accessment of insuline resistance (HOMA) index or circulating free fatty acid levels, limits the comprehensive assessment of adipose tissue metabolism and its potential influence on cardiac performance. While CMR quantification of EAT demonstrated good inter-operator reproducibility, suboptimal image quality forced us to exclude certain patients from the study. Therefore, we chose not to measure atrial EAT and restricted quantification to the ventricles, thereby limiting the interpretation of EAT as a comprehensive tissue. Another limitation of our study is the inability to accurately report the most common causes of death in HFpEF patients, as many deaths occurred outside the hospital setting and were not thoroughly documented in medical records, limiting the comprehensiveness of our mortality analysis.

Conclusions

Our study suggests that increasing EAT volume plays a key role in the development of HFpEF symptoms by influencing cardiac remodeling. Symptomatic HFpEF patients with elevated EAT often have a cardiometabolic profile characterized by diabetes, ischemic cardiomyopathy, and inflammation. These findings point to therapeutic opportunities, such as targeting EAT to prevent HFpEF and intensifying treatment in symptomatic HFpEF patients with a cardiometabolic profile. Combined use of SGLT2 inhibitors and GLP-1 RAs is a promising approach.

Abbreviations

AF	Atrial fibrillation
BMI	Body mass index
cFGF-23	C-terminal fibroblast growth factor-23
CMR	Cardiovascular magnetic resonance
CRP	C-reactive protein
EAT	Epicardial adipose tissue
eSPAP	Estimated systolic pulmonary artery pressures
ECV	Extracellular volume
EDV	End-diastolic volume
eGFR	Estimated glomerular filtration rate
ESV	End-systolic volume
GLS	Global longitudinal strain
GLP-1 RA	Glucagon-like-peptide receptor agonist
GOLD	Global initiative for obstructive lung disease
HF	Heart failure
HFpEF	Heart failure with preserved ejection fraction
HOMA	Homeostasis model accessment of insuline resistance
ICC	Intraclass correlation coefficient
IL	Interleukin
LA	Left atrial
LGE	Late gadolinium enhancement
LV	Left ventricle
LVEF	Left ventricular ejection fraction
NT-proBNP	N-terminal pro-B-type brain natriuretic peptide
NYHA	New York Heart Association
R	R Pearson
RA	Right atrial
SGLT2	Sodium/glucose cotransporter 2
(s)ST2	(Soluble) suppression of tumorigenicity-2
TAPSE	Tricuspid annular plane systolic excursion
T2DM	Type 2 diabetes mellitus
VAT	Visceral adipose tissue

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12933-025-02688-7.

Additional file 1.

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Not applicable.

Author contributions

Anne-Catherine Pouleur (ACP) was the principal investigator of the study and oversaw its design, implementation, and data interpretation. Nassiba Menghoum (NM), Martin Leroy (ML), and Marie Parra (MP) analyzed and interpreted the patient data and drafted the manuscript. NM, Maria Chiara Badia (MCB), Clotilde Roy (CR), and Sibille Lejeune (SL) prospectively recruited patients and collected data. MCB, SL, Agnès Pasquet (AP), David Vancraeynest (DVC), Bernhard L. Gerber (BG), Jean-Luc Balligand (JLB), and Christophe Beauloye (CB) provided advice on data analysis and presentation. ACP, CB, BG, and JLB made substantial contributions to the manuscript's drafting and critical review. For the Beta3-LVH cohort, data acquisition was performed by JLB, Dulce Brito (DB), Barbara Casadei (BC), Christophe Depoix (CD), Frank Edelmann (FE), Vanessa Ferreira (VF), Renaud Lhommel (RL), Masliza Mahmod (MM), Stefan Neubauer (SN), Gerasimos Filippatos (GF), Damien Gruson (DG), Kristian Hellenkamp (KH), Ignatios Ikonomidis (II), Bartosz Krakowiak (BK), Alexandre Persu (AP), Stefan K. Piechnik (SP), Burkert Pieske (BP), Elisabeth Pieske-Kraigher (EPK), Fausto Pinto (FP), Michele Senni (MS), Piotr Ponikowski (PP), Nancy Van Overstraeten (NVO), Rolf Wachter (RW), and ACP. Funding was secured by JLB, Vanessa M. Ferreira (VMF), Burkert Pieske (BP), and Rolf Wachter (RW). All authors reviewed and approved the final version of the manuscript.

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Availability of data and materials

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

The study was approved by the Institutional Review Board of the Cliniques universitaires Saint-Luc, Université Catholique de Louvain, and all participants gave written consent to participate in the study.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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References

1. Schiattarella GG, Rodolico D, Hill JA. Metabolic inflammation in heart failure with preserved ejection fraction. Cardiovasc Res. 2021;117(2):423–34.
2. Packer M, Lam CSP, Lund LH, Maurer MS, Borlaug BA. Characterization of the inflammatory-metabolic phenotype of heart failure with a preserved ejection fraction: a hypothesis to explain influence of sex on the evolution and potential treatment of the disease. Eur J Heart Fail. 2020;22(9):1551–67.
3. Rao VN, Fudim M, Mentz RJ, Michos ED, Felker GM. Regional adiposity and heart failure with preserved ejection fraction. Eur J Heart Fail. 2020;22(9):1540–50.
4. Packer M. Disease-treatment interactions in the management of patients with obesity and diabetes who have atrial fibrillation: the potential mediating influence of epicardial adipose tissue. Cardiovasc Diabetol. 2019;18(1):121.
5. van Woerden G, van Veldhuisen DJ, Westenbrink BD, de Boer RA, Rienstra M, Gorter TM. Connecting epicardial adipose tissue and heart failure with preserved ejection fraction: mechanisms, management and modern perspectives. Eur J Heart Fail. 2022;24(12):2238–50.
6. Oduah MT, Sundaram V, Reddy YN. Epicardial fat in heart failure with preserved ejection fraction: bad actor or just lying around? Card Fail Rev. 2023;9:e06.
7. van Woerden G, van Veldhuisen DJ, Gorter TM, van Empel VPM, Hemels MEW, Hazebroek EJ, et al. Importance of epicardial adipose tissue localization using cardiac magnetic resonance imaging in patients with heart failure with mid-range and preserved ejection fraction. Clin Cardiol. 2021;44(7):987–93.
8. van Woerden G, van Veldhuisen DJ, Manintveld OC, van Empel VPM, Willems TP, de Boer RA, et al. Epicardial adipose tissue and outcome in heart failure with mid-range and preserved ejection fraction. Circ Heart Fail. 2022;15(3):e009238.
9. Kenchaiah S, Ding J, Carr JJ, Allison MA, Budoff MJ, Tracy RP, et al. Pericardial fat and the risk of heart failure. J Am Coll Cardiol. 2021;77(21):2638–52.
10. Rao VN, Bush CG, Mongraw-Chaffin M, Hall ME, Clark D 3rd, Fudim M, et al. Regional adiposity and risk of heart failure and mortality: the jackson heart study. J Am Heart Assoc. 2021;10(14):e020920.
11. Mahabadi AA, Anapliotis V, Dykun I, Hendricks S, Al-Rashid F, Lüdike P, et al. Epicardial fat and incident heart failure with preserved ejection fraction in patients with coronary artery disease. Int J Cardiol. 2022;357:140–5.
12. Gorter TM, van Woerden G, Rienstra M, Dickinson MG, Hummel YM, Voors AA, et al. Epicardial adipose tissue and invasive hemodynamics in heart failure with preserved ejection fraction. JACC Heart Fail. 2020;8(8):667–76.
13. Bozkurt B, Coats AJS, Tsutsui H, Abdelhamid CM, Adamopoulos S, Albert N, et al. Universal definition and classification of heart failure: a report of the heart failure society of America, heart failure association of the European society of cardiology, Japanese heart failure society and writing committee of the universal definition of heart failure: endorsed by the Canadian heart failure society, heart failure association of India, cardiac society of Australia and New Zealand, and chinese heart failure association. Eur J Heart Fail. 2021;23(3):352–80.
14. Bayes-Genis A, Bisbal F, Nunez J, Santas E, Lupon J, Rossignol P, et al. Transitioning from preclinical to clinical heart failure with preserved ejection fraction: a mechanistic approach. J Clin Med. 2020;9(4):1110.
15. Pouleur AC, Menghoum N, Cumps J, Marino A, Badii M, Lejeune S, et al. Plasma myo-inositol elevation in heart failure: clinical implications and prognostic significance. Results from the BElgian and CAnadian MEtabolomics in HFpEF (BECAME-HF) research project. EBioMedicine. 2024; 107: 105264.
16. Sun Y, Wang N, Li X, Zhang Y, Yang J, Tse G, et al. Predictive value of H(2) FPEF score in patients with heart failure with preserved ejection fraction. ESC Heart Fail. 2021;8(2):1244–52.
17. Araújo SP, Juvanhol LL, Bressan J, Hermsdorff HHM. Triglyceride glucose index: a new biomarker in predicting cardiovascular risk. Prev Med Rep. 2022;29: 101941.
18. Balligand JL, Brito D, Brosteanu O, Casadei B, Depoix C, Edelmann F, et al. Repurposing the beta3-adrenergic receptor agonist mirabegron in patients with structural cardiac disease: the beta3-LVH Phase 2b randomized clinical trial. JAMA Cardiol. 2023;8(11):1031–40.
19. Pouleur AC, Anker S, Brito D, Brosteanu O, Hasenclever D, Casadei B, et al. Rationale and design of a multicentre, randomized, placebo-controlled trial of mirabegron, a Beta3-adrenergic receptor agonist on left ventricular mass and diastolic function in patients with structural heart disease Beta3-left ventricular hypertrophy (Beta3-LVH). ESC Heart Fail. 2018;5(5):830–41.
20. Roy C, Slimani A, de Meester C, Amzulescu M, Pasquet A, Vancraeynest D, et al. Associations and prognostic significance of diffuse myocardial fibrosis by cardiovascular magnetic resonance in heart failure with preserved ejection fraction. J Cardiovasc Magn Reson. 2018;20(1):55.
21. Borlaug BA, Jensen MD, Kitzman DW, Lam CSP, Obokata M, Rider OJ. Obesity and heart failure with preserved ejection fraction: new insights and pathophysiological targets. Cardiovasc Res. 2023;118(18):3434–50.
22. Shi YJ, Dong GJ, Guo M. Targeting epicardial adipose tissue: a potential therapeutic strategy for heart failure with preserved ejection fraction with type 2 diabetes mellitus. World J Diabetes. 2023;14(6):724–40.
23. Zain S, Shamshad T, Kabir A, Khan AA. Epicardial adipose tissue and development of atrial fibrillation (AFIB) and heart failure with preserved ejection fraction (HFpEF). Cureus. 2023;15(9): e46153.
24. Sousa JA, Mendonça MI, Serrão M, Borges S, Henriques E, Freitas S, et al. Epicardial adipose tissue: the genetics behind an emerging cardiovascular risk marker. Clin Med Insights Cardiol. 2021;15:11795468211029244.
25. Iacobellis G. aging effects on epicardial adipose tissue. Front Aging. 2021;2:666260.
26. Li Y, Liu B, Li Y, Jing X, Deng S, Yan Y, et al. Epicardial fat tissue in patients with diabetes mellitus: a systematic review and meta-analysis. Cardiovasc Diabetol. 2019;18(1):3.
27. Packer M. Epicardial adipose tissue may mediate deleterious effects of obesity and inflammation on the myocardium. J Am Coll Cardiol. 2018;71(20):2360–72.
28. Greulich S, Maxhera B, Vandenplas G, de Wiza DH, Smiris K, Mueller H, et al. Secretory products from epicardial adipose tissue of patients with type 2 diabetes mellitus induce cardiomyocyte dysfunction. Circulation. 2012;126(19):2324–34.
29. Anthony SR, Guarnieri AR, Gozdiff A, Helsley RN, Phillip Owens A, Tranter M. Mechanisms linking adipose tissue inflammation to cardiac hypertrophy and fibrosis. Clin Sci. 2019;133(22):2329–44.

30. Pezeshkian M, Mahtabipour MR. Epicardial and subcutaneous adipose tissue Fatty acids profiles in diabetic and non-diabetic patients candidate for coronary artery bypass graft. Bioimpacts. 2013;3(2):83–9.
31. Goldman SA, Requena-Ibanez JA, Devesa A, Santos-Gallego CG, Badimon JJ, Fuster V. Uncovering the role of epicardial adipose tissue in heart failure with preserved ejection fraction. JACC Adv. 2023;2(9): 100657.
32. Imoto-Tsubakimoto H, Takahashi T, Ueyama T, Ogata T, Adachi A, Nakanishi N, et al. Serglycin is a novel adipocytokine highly expressed in epicardial adipose tissue. Biochem Biophys Res Commun. 2013;432(1):105–10.
33. Gaborit B, Venteclef N, Ancel P, Pelloux V, Gariboldi V, Leprince P, et al. Human epicardial adipose tissue has a specific transcriptomic signature depending on its anatomical peri-atrial, peri-ventricular, or peri-coronary location. Cardiovasc Res. 2015;108(1):62–73.
34. Pascual-Figal DA, Januzzi JL. The biology of ST2: the international ST2 consensus panel. Am J Cardiol. 2015;115(7 Suppl):3b–7b.
35. Vianello E, Dozio E, Bandera F, Schmitz G, Nebuloni M, Longhi E, et al. Dysfunctional EAT thickness may promote maladaptive heart remodeling in CVD patients through the ST2-IL33 system, directly related to EPAC protein expression. Sci Rep. 2019;9(1):10331.
36. Mason T, Coelho-Filho OR, Verma S, Chowdhury B, Zuo F, Quan A, et al. Empagliflozin reduces myocardial extracellular volume in patients with type 2 diabetes and coronary artery disease. JACC Cardiovasc Imaging. 2021;14(6):1164–73.
37. Sato T, Aizawa Y, Yuasa S, Kishi S, Fuse K, Fujita S, et al. The effect of dapagliflozin treatment on epicardial adipose tissue volume. Cardiovasc Diabetol. 2018;17(1):6.
38. Masson W, Lavalle-Cobo A, Nogueira JP. Effect of SGLT2-Inhibitors on epicardial adipose tissue: a meta-analysis. Cells. 2021;10(8):2150.
39. Zelniker TA, Bonaca MP, Furtado RHM, Mosenzon O, Kuder JF, Murphy SA, et al. Effect of Dapagliflozin on atrial fibrillation in patients with type 2 diabetes mellitus: insights from the DECLARE-TIMI 58 trial. Circulation. 2020;141(15):1227–34.
40. Iacobellis G, Baroni MG. Cardiovascular risk reduction throughout GLP-1 receptor agonist and SGLT2 inhibitor modulation of epicardial fat. J Endocrinol Invest. 2022;45(3):489–95.
41. Anker SD, Butler J, Filippatos G, Ferreira JP, Bocchi E, Böhm M, et al. Empagliflozin in heart failure with a preserved ejection fraction. N Engl J Med. 2021;385(16):1451–61.
42. Solomon SD, McMurray JJV, Claggett B, de Boer RA, DeMets D, Hernandez AF, et al. Dapagliflozin in heart failure with mildly reduced or preserved ejection fraction. N Engl J Med. 2022;387(12):1089–98.
43. Borlaug BA, Kitzman DW, Davies MJ, Rasmussen S, Barros E, Butler J, et al. Semaglutide in HFpEF across obesity class and by body weight reduction: a prespecified analysis of the STEP-HFpEF trial. Nat Med. 2023;29(9):2358–65.
44. Pugliese NR, Paneni F, Mazzola M, De Biase N, Del Punta L, Gargani L, et al. Impact of epicardial adipose tissue on cardiovascular haemodynamics, metabolic profile, and prognosis in heart failure. Eur J Heart Fail. 2021;23(11):1858–71.
45. Wu A, Yang Z, Zhang X, Lin Z, Lu H. Association between epicardial adipose tissue and left atrial and ventricular function in patients with heart failure: a systematic review and meta-analysis. Curr Probl Cardiol. 2023;48(12): 101979.
46. Liu J, Yu Q, Li Z, Zhou Y, Liu Z, You L, et al. Epicardial adipose tissue density is a better predictor of cardiometabolic risk in HFpEF patients: a prospective cohort study. Cardiovasc Diabetol. 2023;22(1):45.
47. Lejeune S, Roy C, Slimani A, Pasquet A, Vancraeynest D, Beauloye C, et al. Heart failure with preserved ejection fraction in Belgium: characteristics and outcome of a real-life cohort. Acta Cardiol. 2021;76(7):697–706.

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