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Epicardial adipose tissue thickness is associated with reduced peak oxygen consumption and systolic reserve in patients with type 2 diabetes and normal heart function

Lorenzo Nesti MD[1,2] | Nicola Riccardo Pugliese PhD[2] | Martina Chiriacò MD[1,2] | Domenico Trico MD[1] | Simona Baldi PhD[1] | Andrea Natali MD[1,2]

[1]Metabolism, Nutrition, and Atherosclerosis Laboratory, Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy

[2]Cardiopulmonary Laboratory, Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy

Correspondence
Lorenzo Nesti, MD, Dipartimento di Medicina Clinica e Sperimentale, Università di Pisa, Via Savi 27, 56100 Pisa, Italy.
Email: lorenzo.nesti@phd.unipi.it

Abstract

Aim: To investigate the impact of epicardial adipose tissue (EAT) thickness on cardiopulmonary performance in patients with type 2 diabetes (T2D) and normal heart function.

Materials and methods: We analysed EAT thickness in subjects with T2D and normal biventricular systo-diastolic functions undergoing a maximal cardiopulmonary exercise test combined with stress echocardiography, speckle tracking and pulmonary function assessment, as well as serum N-terminal pro B-type natriuretic peptide (NT-proBNP).

Results: In the 72 subjects enrolled, those with EAT thickness above the median (> 5 mm) showed higher body fat mass, smaller indexed left ventricular dimensions and marginally reduced diastolic function variables at rest. Higher EAT thickness was associated with lower peak oxygen uptake (VO_{2peak} 17.1 ± 3.6 vs. 21.0 ± 5.7 ml/min/kg, $P = .001$), reduced systolic reserve (ΔS′ 4.6 ± 1.6 vs. 5.8 ± 2.5 m/s, $P = .02$) and higher natriuretic peptides (NT-proBNP 64 [29-165] vs. 31 [26-139] pg/ml, $P = .04$), as well as chronotropic insufficiency and impaired heart rate recovery. Ventilatory variables and peripheral oxygen extraction were not different between groups. EAT was independently associated with VO_{2peak} and linearly and negatively correlated with peak heart rate, heart rate recovery, workload, VO_2 at the anaerobic threshold and at peak, and cardiac power output, and was directly correlated with natriuretic peptides.

Conclusion: Higher EAT thickness in T2D is associated with worse cardiopulmonary performance and multiple traits of subclinical cardiac systolic dysfunction.

KEYWORDS

cardiopulmonary exercise test, cardiopulmonary fitness, diabetic cardiomyopathy, echocardiography, effort intolerance, epicardial adipose tissue, heart failure with preserved ejection fraction, type 2 diabetes

Lorenzo Nesti and Nicola Riccardo Pugliese contributed equally to this study.

1 | INTRODUCTION

Individuals with type 2 diabetes (T2D) are at a high risk of developing heart failure with preserved ejection fraction (HFpEF), a heterogeneous and complex syndrome that, despite its growing prevalence and incidence with significant morbidity and mortality, still retains important knowledge gaps and therapeutic challenges.[1] In recent years, excessive epicardial adipose tissue (EAT) has been regarded as a one among the main actors in myocardial disease by promoting inflammation, micro-vasculopathy, fibrosis and stiffness of myocardium, all findings corresponding to the hallmarks of HFpEF.[2] Its quantification is easy and reproducible during standard transthoracic echocardiography.[3] However, its role in cardiovascular and metabolic disorders remains understudied.

Subjects with T2D exhibit higher EAT thickness than controls, both free from heart disease[4] and with overt heart failure (HF).[5] In T2D, hypertrophied EAT produces pro-inflammatory cytokines[6] and has been associated with impaired cardiomyocyte metabolism and contractile function,[7] systo-diastolic dysfunction[4] and raised circulating biomarkers of myocardial damage.[5] Given its consistent prognostic power both in HF without T2D[8] and in T2D without HF,[4] EAT probably plays a key role in the progression to overt HF. Nonetheless, the relationship between EAT thickness and cardiopulmonary performance in T2D without heart disease has never been evaluated.[9]

By using an imaging-cardiopulmonary exercise test (iCPET), the current study aimed to evaluate the association of echocardiography-assessed EAT thickness with heart structure and contractility (as measured by resting and exercise 2D-echo, Doppler, and speckle-tracking technology) and cardiopulmonary fitness (pulmonary, metabolic, and haemodynamic variables during graded, maximal cycloergometer exercise) in T2D patients without HF and with normal biventricular systo-diastolic function. We also tested whether EAT thickness is associated with plasma biomarkers of inflammation, oxidative stress, matrix remodelling, and myocyte strain and injury in a subgroup of patients, aiming to identify the pathophysiological mechanisms at play.

2 | MATERIALS AND METHODS

2.1 | Study population

We prospectively enrolled patients from the Diabetes Outpatient Clinic at the Santa Chiara University Hospital of Pisa. The local Ethics Committee approved the study protocol. All patients gave written informed consent. Inclusion criteria: men or women up to 80 years of age with a clinical diagnosis of T2D according to American Diabetes Association criteria[10]; on stable hypoglycaemic and cardioactive therapy for the previous 3 months; baseline left ventricle ejection fraction (LVEF) above 50%; without a diagnosis of HF according to European Society of Cardiology (ESC) guidelines,[1,11] including HFpEF according to the Heart Failure Association PEFF diagnostic algorithm.[1] Exclusion criteria: symptoms or diagnosis of HF, any established current cardiac disease including previous cardiovascular events, coronary artery disease, uncontrolled arrhythmias (including atrial [LA] fibrillation) and/or any more than mild valvular disease; respiratory insufficiency or diagnosis of chronic obstructive pulmonary disease (more than moderate airflow obstruction [forced expiratory volume in 1 second {FEV1} to forced vital capacity {FVC} ratio < 0.70 and FEV1 < 50% of predicted FEV1] and/or restrictive pattern [< 80% of predicted FVC]); pulmonary hypertension; any acute or chronic inflammatory disease; uncontrolled blood pressure defined as blood pressure (BP) more than 160/100 mmHg; severely impaired kidney function defined as an estimated glomerular filtration rate (eGFR) of less than 30 ml/min/1.73m^2; inability to cycle because of physical limitations and/or unable to perform a maximal exercise test; poor echocardiographic acoustic windows; ongoing pregnancy or breastfeeding.

2.2 | Patient characterization

2.2.1 | Clinical and biohumoral characterization

A full clinical history was obtained. Baseline demographic data, anthropometric variables (height, weight and body mass index [BMI]), functional status, cardiovascular risk factors (e.g. alcohol consumption and smoking habits), co-morbidities (e.g. arterial hypertension, dyslipidaemia), diabetic complications (microvascular and/or macrovascular) and medication were also recorded. Statin therapy intensity was classified as low (simvastatin 10-to-20 mg/day or atorvastatin 10 mg/day), medium (simvastatin 40 mg/day or atorvastatin 20 mg/day or rosuvastatin 5 mg/day) or high intensity (atorvastatin 40-to-80 mg/day or rosuvastatin 20-to-40 mg/day). A thorough physical examination was also performed, including resting vital variables. We calculated lean body mass with Boer's formula.[12]

Blood cell count, HbA1c, blood lipids, creatinine, electrolytes, uric acid, hepatic function, urinalysis and urine albumin-to-creatinine ratio were recorded at baseline. eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula.

2.2.2 | Vascular assessment

Patients underwent peripheral vascular disease assessment through the cardio-ankle vascular index and ankle-brachial index with the Vascular Screening System VaSera VS-1500N (Fukuda Denshi, Japan) to rule out peripheral vascular disease. Endothelial function was assessed by downstream hyperaemic response to ischaemia using an EndoPAT device (EndoPAT 2000; Itamar Medical Ltd, Caesarea, Israel), according to standard procedures.[13] The reactive hyperaemia index was calculated as the ratio between postocclusion and preocclusion amplitudes of the pulse, normalized to the contralateral arm.

2.2.3 | Diagnosis of cardiac autonomic neuropathy

Screening of cardiac autonomic neuropathy (CAN) was performed with a Meteda neurotester (San Benedetto del Tronto, Italy):

variations in RR intervals in response to the Valsalva manoeuvre, lying-to-standing, and deep breathing were analysed according to standard procedures.[14] The three tests were repeated three times for each patient. Two or more abnormal tests, based on age-related normal values, identified the presence of CAN.

2.3 | Cardiopulmonary exercise test protocol

A symptom-limited graded ramp bicycle exercise test was performed in the semi-supine position on a tilting, dedicated, microprocessor-controlled stress echocardiography cycle ergometer (Ergoline ergoselect 2000 GmbH, Germany). A 12-lead electrocardiogram and non-invasive arterial saturation and BP were monitored continuously. Heart rate (HR) and brachial BP were measured at rest and every minute during exercise using a validated automatic device (Omron M6 Comfort, Kyoto, Japan). The expected oxygen uptake at peak exercise (VO_{2peak}), estimated on the basis of patient age, height, weight and clinical history,[15] was used to adjust the ramp increments (W) to reach the patient's estimated VO_{2peak} in 10 to 12 minutes. The protocol included 2 minutes of unloaded pedalling and 4 minutes of recovery after peak effort. CPET performance was only considered for analysis if maximal, as defined by a peak respiratory exchange ratio steadily above 1.10 at peak exercise, as per protocol. Breath-by-breath minute ventilation, carbon dioxide production (VCO_2) and VO_2 were measured using a dedicated cardiopulmonary diagnostic device (Blue Cherry, Geratherm Respiratory GmbH, Germany). We defined VO_{2peak} as the highest median value of the two 30-second intervals of the last minute of exercise, as previously validated.[16] An automatic procedure determined anaerobic threshold (AT) based on the V-slope, ventilatory equivalents and end-tidal partial pressure methods; AT was verified visually and, if necessary, recalculated.[15] The chronotropic response was calculated as the change in HR from rest to peak exercise, divided by the difference between the age-predicted maximal HR and the resting HR (i.e. HR reserve). Chronotropic incompetence was defined as the failure to achieve 80% or more of the HR reserve during exercise.[17] In patients on β-blockers or calcium-channel blockers, chronotropic incompetence was defined as the failure to achieve 62% of HR reserve.[17]

2.4 | Baseline, speckle tracking and exercise stress echocardiography protocol

All patients underwent a comprehensive transthoracic echocardiography examination at rest (GE Healthcare Vivid E95, Milwaukee, WI) according to international recommendations.[18] Data collected at each stage, that is, at baseline, after 4 minutes, at the AT, and at peak effort, included: left ventricle (LV) and LA volumes, stroke volume (SV), peak E-wave and A-wave velocities, tissue Doppler imaging (TDI)-derived S′ and e′ at the septal and lateral mitral annulus, tricuspid regurgitation velocity and systolic pulmonary artery pressure, tricuspid annular plane systolic excursion; LV volumes and LVEF were calculated from the apical two- and four-chamber views using the modified Simpson's rule. SV was calculated by multiplying the LV outflow tract area at rest by the LV outflow tract velocity-time integral measured by pulsed-wave Doppler during each activity level, as previously validated. Cardiac output (CO) was calculated as the multiplication of SV and HR. Cardiac power output (CPO) was measured with the following formula: $\mathrm{CPO} = 0.222 \times CO\left[\frac{\mathrm{L}}{\mathrm{min}}\right] \times \mathrm{mean\ BP\,[mmHg]}$.[19] The $\Delta(a\text{-}v)O_2$ was estimated indirectly with a validated and previously used approach.[20] Images were acquired concurrently with breath-by-breath gas exchange measurements at both baseline and peak of exercise. All measurements were reported as the average of three beats.

We measured global longitudinal strain (GLS) from the apical long-axis view and two- and four-chamber views, ensuring a frame rate of more than 50 Hz (GE Healthcare EchoPAC BT 12) through speckle-tracking technology. We reported the average values from the three apical views at rest and low-load effort, within the first 4 minutes of exercise. We excluded poorly tracked segments and patients were not analysed if more than one segment per view was deemed unacceptable. Speckle-tracking technology-derived measurements were reported as the average of three beats.

2.5 | Measurement of EAT thickness

EAT thickness was measured on the free wall of the right ventricle from the parasternal long-axis view at end-systole, as previously described,[21] averaged from two cardiac cycles and using imaging constraints to ensure that the EAT thickness was not measured obliquely, attempting to be perpendicular to the aortic annulus, which was used as an anatomical landmark. EAT appears as an echo-free or hyperechoic space. Maximal thickness was recorded as a linear measure (in millimetres) with the lead-to-lead technique of the maximal thickness at this point (Figure 1). Its measurement on the right ventricle was chosen for two reasons: (a) this point is recognized as the highest absolute EAT layer thickness; and (b) parasternal long- and short-axis views allow the most accurate measurement of EAT on the right ventricle, with optimal cursor beam orientation in each view.

2.6 | Plasma biomarkers

Plasma biomarkers were chosen as markers of (a) inflammation: tumour necrosis factor-alpha (TNFa) and (b) high-sensitive c-reactive protein (hsCRP); (c) LV parietal stress: natriuretic peptides (brain natriuretic peptide [BNP] and N-terminal pro B-type natriuretic peptide [NT-proBNP]), pro-adrenomedullin (proADM); (d) cardiomyocyte damage: high-sensitive troponin T (hsTnT); and (e) extracellular matrix remodelling/fibrosis: procollagen (NT-PRO3). TNFa and hsCRP were measured by ELISA kits (TNF-alpha human, high-sensitivity and CRP Human; Invitrogen, ThermoFisher Scientific, MA). hsTnT, BNP and NT-pro BNP were assayed by ECLIA methodology using Elecsys commercial kits (Troponin T hs, BNP and proBNP II, respectively; Roche Diagnostics, Milan, Italy) on a COBAS e411 analyser. Mid-regional proADM and NT-PRO3 were measured by ELISA kits (Human MR-ProADM and Human Procollagen III N-Terminal Propeptide, respectively; MYBIOSOURCE, San Diego, CA).

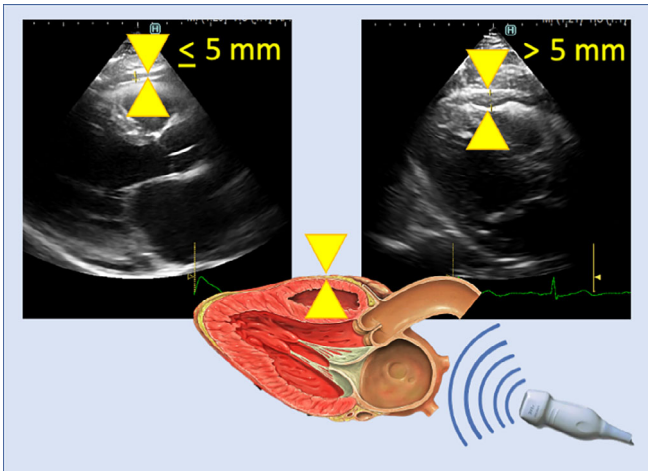

FIGURE 1 Measurement of epicardial adipose tissue (EAT) thickness. EAT appears as an echo-free or hypoechoic space outside the free wall of the outflow tract of the right ventricle from the parasternal long-axis view at end-systole. Maximal thickness was recorded as a linear measure (millimetres) perpendicular to the aortic annulus. Patients were divided based on their ranking above and below the median value (5 mm). The left panel reports a frame from a patient with an EAT thickness of less than 5 mm; the right panel shows a frame from a patient with an EAT thickness above 5 mm

2.7 | Statistical analysis

Values are presented as mean ± standard deviation, or as median and interquartile range (IQR), for variables with normal and non-normal distribution, respectively. Variables with a non-normal distribution using the Kolmogorov-Smirnov test were logarithmically transformed for parametric analysis. Comparisons between groups were made by the Student *t*-test for unpaired data for continuous variables and by the chi-square test or ANOVA for categorical variables.

Factors with ascertained or potential influence on EAT thickness and on VO_{2peak} (age, sex, BMI, duration of diabetes, HbA1c, eGFR, hsCRP) were tested. Given the difference in BMI between the two study groups, we calculated and used VO_{2peak} normalized for lean body weight. Univariate linear regressions between EAT thickness and the main iCPET values and plasma biomarkers were analysed. We constructed a multivariate model for predictors of VO_{2peak} that included age, BMI, sex and resting GLS.

Analyses were performed using JMP Pro software version 13.2.1 (SAS Institute, Cary, NC). All tests were conducted at a two-sided α level of .05. A *P* value of less than .05 was considered statistically significant.

3 | RESULTS

3.1 | Study population

According to inclusion and exclusion criteria we prospectively enrolled 72 subjects, whose baseline characteristics are reported in Table 1. Patients were middle-aged, mainly males, with suboptimal glycaemic control, and with a low prevalence of microvascular complications and a negligible prevalence of previous cerebrovascular events. Baseline physical activity was recorded via a medical interview at baseline. Patients were all sedentary or moderately active (walking); no patients were exercising regularly (more than once per week) at the time of enrolment. Generally, blood pressure control was suboptimal. Based on the ranking of EAT thickness (median 5 mm), we divided the population in two subgroups of 36 subjects each (Figure 1) who showed comparable age, sex distribution, duration of diabetes, smoking habit, alcohol intake, co-morbidities, prevalence of complications and medications. The group with higher EAT thickness showed higher fat body mass with a higher proportion of obese subjects than the other group, which mainly consisted of overweight individuals. A more frequent use of antiplatelet agents and medium-intensity statin therapy was also present, despite comparable cardiovascular risk scores (ESC score 2.7 ± 1.6 vs. 3.1 ± 1.7; pooled cohort equations 27.1 ± 14.8 vs. 22.8 ± 14.2, $P = .1253$), use of total antihypertensive drugs, blood pressure values and prevalence of previous cerebrovascular events.

3.2 | Biohumoral, vascular and autonomic characterization

The two groups showed comparable glycaemic control (HbA1c), renal function, albuminuria, haemoglobin and uric acid, while total cholesterol and LDL cholesterol were lower in those with higher EAT thickness. No difference between the groups was observed in either vascular variables (vascular stiffness and endothelial function) or prevalence of autonomic dysfunction at rest. Specifically, no significant difference was observed among autonomic variables between the groups, either using the individual score (in its continuous range 0-6) or the RR ratio of each test. Results are reported in Table 1.

3.3 | Cardiopulmonary exercise test

All patients reached maximal exercise as required by the inclusion criteria, and the duration of exercise was between 10 and 12 minutes as per protocol, with no difference between the two groups. The exercise was well-tolerated without chest discomfort, hypertensive response or any significant alteration in either vital variables or ECG trace. The results are reported in Table 2 and Figure 2. Altogether, patients with higher EAT thickness displayed lower effort tolerance with a 19% lower maximal VO_2 and reached at 13% lower mean workload. VO_2 was also 8% lower at the anaerobic threshold and the VO_2/work slope was slightly reduced (10.2 ± 1.2 vs. 11.0 ± 1.6, $P = .0409$) with respect to those with lower EAT thickness. Also, the chronotropic response was impaired in the thicker EAT group, as was evident from the lower HR at peak exercise, the higher prevalence of chronotropic insufficiency, and the slower HR decline 1 minute after the end of the exercise.

TABLE 1 Baseline characteristics of the study population[a]

	All patients (n = 72)	Epicardial adipose tissue		P value
		≤ 5 mm (n = 36)	> 5 mm (n = 36)	
Clinical and anthropometric variables				
Male gender (n, %)	57 (79%)	29 (81%)	28 (78%)	ns
Age (y)	63.3 ± 8.7	62.1 ± 8.5	64.4 ± 8.9	ns
BMI (kg/m^2)	28.9 ± 4.7	27.4 ± 4.3	29.9 ± 5.0	.0059
BMI < 25 kg/m^2 (n, %)	14 (19%)	11 (31%)	3 (8%)	–
BMI 25-30 kg/m^2 (n, %)	32 (44%)	18 (50%)	14 (39%)	–
BMI > 30 kg/m^2 (n, %)	26 (36%)	7 (19%)	19 (53%)	.0050
Lean body weight (kg)	58.7 ± 8.4	58.1 ± 7.4	59.3 ± 9.4	ns
Fat body weight (kg)	24.7 ± 8.5	22.2 ± 7.5	27.3 ± 8.7	.0089
Abdominal circumference (cm)	101.3 ± 10.7	99.6 ± 11.4	103.5 ± 9.5	ns
Systolic BP (mmHg)	138.9 ± 14.7	138.3 ± 16.9	139.5 ± 12.3	ns
Diastolic BP (mmHg)	86.5 ± 9.6	85.9 ± 9.7	87.0 ± 9.7	ns
Alcohol (n, %)	3 (4%)	1 (3%)	2 (6%)	ns
Active smokers (n, %)	11 (15%)	6 (17%)	5 (15%)	ns
Hypertension (n, %)	55 (76%)	25 (69%)	30 (81%)	ns
Dyslipidaemia (n, %)	54 (75%)	25 (69%)	30 (81%)	ns
Duration of diabetes (y)	9.6 ± 7.9	9.4 ± 6.4	9.8 ± 9.3	ns
Previous cerebrovascular event	6 (9)	1 (3)	5 (15)	ns
Microvascular complications	18 (25)	6 (17)	12 (33)	ns
Therapy				
ACEi/ARBs (n, %)	45 (63%)	19 (53%)	26 (72%)	ns
Beta-blockers (n, %)	19 (26%)	10 (28%)	9 (25%)	ns
Mineralocorticoid receptor antagonist (n, %)	2 (3%)	1 (3%)	1 (3%)	ns
Diuretics (n, %)	13 (18)	4 (11)	9 (25)	ns
Ca antagonist (n, %)	17 (24)	6 (17%)	11 (31%)	ns
Antiplatelet (n, %)	24 (33)	7 (19%)	17 (47%)	.0114
Allopurinol (n, %)	6 (8)	2 (6%)	4 (11%)	ns
Statin (n, %)	50 (69%)	23 (64%)	27 (75%)	ns
Low intensity	23 (31)	14 (37)	9 (25)	ns
Medium intensity	20 (27)	6 (16)	14 (39)	.0350
High intensity	10 (14)	5 (13)	5 (14)	ns
Metformin, n (%)	62 (86%)	30 (83%)	32 (89%)	ns
GLP-1 RA (n, %)	2 (3%)	0 (0%)	2 (4%)	ns
DPP4i (n, %)	2 (3%)	2 (4%)	0 (0%)	ns
SGLT2i (n, %)	0 (0%)	0 (0%)	0 (0%)	ns
Insulin (n, %)	12 (17%)	9 (25%)	3 (8%)	ns
Biohumoral characterization				
HbA1c (mmol/mol)	57.0 ± 10.5	58.4 ± 11.6	55.6 ± 9.1	ns
Cholesterol (mg/dl)	166.9 ± 39.8	176.7 ± 43.7	157.0 ± 33.4	.0350
HDL-c (mg/dl)	50.0 ± 13.4	52.0 ± 14.3	47.8 ± 12.2	ns
LDL-c (mg/dl)	102.6 ± 33.2	112.5 ± 35.88	92.8 ± 27.3	.0108
Triglycerides (mg/dl)	129.6 ± 61.7	124.9 ± 68.4	134.3 ± 54.9	ns
Haemoglobin (g/dl)	14.2 ± 1.3	14.3 ± 1.1	14.0 ± 1.5	ns
Creatinine (mg/dl)	0.88 ± 0.19	0.85 ± 0.16	0.91 ± 0.21	ns
eGFR calculated using CKD-EPI (ml/min/1.73m^2)	87.7 ± 15.4	90.4 ± 11.9	84.8 ± 18.0	ns

(Continues)

TABLE 1 (Continued)

	All patients (n = 72)	Epicardial adipose tissue		
		≤ 5 mm (n = 36)	> 5 mm (n = 36)	*P* value
Uric acid (mg/dl)	5.36 ± 1.41	5.28 ± 1.73	5.43 ± 1.10	ns
Vascular and autonomic function				
RHI endoPAT	0.62 ± 0.28	0.67 ± 0.33	0.61 ± 0.25	ns
CAN (n, %)	5 (7)	2 (10)	3 (14)	ns
CAVI mean	9.32 ± 1.59	9.24 ± 1.90	9,93 ± 1.47	ns

[a]The study population is reported as a whole and divided into two groups based on EAT thickness above or below the median (5 mm). *P* values were calculated with a Student *t*-test for paired data and chi-squared test for nominal variables, and are reported as "ns" if non-significant.
Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; BP, blood pressure; CAN, cardiac autonomic neuropathy; CAVI, cardio-ankle vascular index; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; DPP4i, dipeptidyl peptidase-4 inhibitor; EAT, epicardial adipose tissue; eGFR, estimated glomerular filtration rate; GLP-1 RA, glucagon-like peptide-1 receptor agonist; RHI, reactive hyperaemia index; SGLT2i, sodium-glucose co-transporter-2 inhibitor.

3.4 | Resting and exercise echocardiography

All patients had normal chamber dimensions and systo-diastolic function with LVEF more than 50%. The results are reported in Table 2 and Figure 2. The group with higher EAT thickness displayed lower indexed LV linear dimensions (despite showing comparable indexed end-diastolic volume) and lower resting E/A ratio with respect to the other group. During exercise, higher EAT thickness was associated with reduced systolic reserve as expressed by reduced ΔS′ and impaired cardiac power output adaptation (ΔCPO, from rest to peak exercise). The other measured values, including cardiac output, other diastolic variables (e′ mean and E/e′ ratio), 2D-LVEF, and resting and exercise LV-GLS, were comparable between the two groups.

3.5 | Plasma biomarkers

A significant difference was observed in plasma BNP and NT-proBNP concentrations between the two groups, with higher values in those with thicker EAT. The other plasma biomarkers (hsCRP, TnHS, pro-ADM, NT-PRO3 and TNFa) showed no difference between groups. The results are reported in Table 2.

3.6 | Univariate and multivariate analysis

At univariate linear regression analysis (Figure 3), EAT thickness negatively correlated with workload, VO_{2peak}, CPO at peak, HR at peak and ΔCPO. Among serum biomarkers, a direct relationship was observed between EAT thickness and BNP.

Multivariate analysis showed that EAT is independently associated with VO_{2peak} after correction for known and potential confounders (stB −0.30, $P = .007$) and that this relationship is not modulated by BMI (EAT*BMI interaction effect: stB 0.13, $P = .181$). As for definition, this statistical approach cannot show interaction, but cannot exclude it as well; still, the correction for potential confounders strengthens this plausibility. In the complete multivariate model (R^2 0.416, $P < .0001$), VO_{2peak} was determined to be 17.5% by EAT thickness (partial R^2 0.073).

4 | DISCUSSION

The current study aimed to verify whether increased EAT thickness is associated with haemodynamic, ventilatory, metabolic and plasma biomarkers abnormalities in subjects with T2D without heart disease undergoing a maximal iCPET, in accordance with the multimodality imaging approach suggested by the recent guidelines on the study of left ventricular dysfunctions in diabetes.[22]

No reference values for EAT thickness are provided in the literature; nonetheless, the median value of our population (5 mm) is in line with previous reports and coincides with the proposed cut-off that has been associated with worse outcome and more pronounced cardiopulmonary derangements in HFpEF.[8] It is known that EAT thickness is higher in T2D than in controls and increases with age and obesity.[23] In alignment with the literature, we found higher fat mass and prevalence of obesity with higher EAT thickness, despite comparable estimated lean body weight, waist circumference, age and sex prevalence. No correlation with vascular and/or autonomic function, duration of diabetes, prevalence of complications (both microvascular and macrovascular), smoking habits and/or alcohol intake and co-morbidities was observed. The more frequent use of antiplatelet and cholesterol-lowering drugs possibly reflects the slightly higher (yet non-significant, possibly secondary to the modest sample size with limited power to detect differences between groups) prevalence of carotid atherosclerosis and cerebrovascular events in this group, also justifying the association between lower total and LDL-cholesterol levels and the more frequent use of moderate-intensity statin therapy.

EAT thickness was associated with smaller indexed LV chamber, an association (interestingly, including aortic root dimensions[24]) previously shown in both HFpEF[8] and in subjects without HF,[25-27] and confirmed by a meta-analysis.[28] We also detected a lower E/A ratio at rest in the group with higher EAT thickness, despite comparable E,

TABLE 2 Results of cardiopulmonary exercise test, exercise echocardiography and plasma biomarkers[a]

	All patients (n = 72)	Epicardial adipose tissue		
		≤ 5 mm (n = 36)	• > 5 mm (n = 36)	*P* value
Cardiopulmonary exercise test				
Workload (W)	119 ± 30	127 ± 32	111 ± 27	.0243
Time of effort (min)	11.3 ± 2.0	11.4 ± 2.1	11.2 ± 2.0	ns
HR rest (bpm)	79.8 ± 13.8	77.8 ± 12.4	81.8 ± 15.1	ns
HR at AT (bpm)	120.0 ± 17.7	123.1 ± 16.8	116.6 ± 18.3	ns
HR peak (bpm)	133.8 ± 18.7	138.9 ± 17.7	128.7 ± 18.4	.0197
HR peak (%max)	86.3 ± 11.7	88.7 ± 11.0	83.8 ± 12.0	ns
HR reserve (bpm)	75.4 ± 15.2	78.9 ± 12.6	71.9 ± 16.9	.0489
Chronotropic incompetence (n, %)	37 (51%)	14 (39%)	23 (64%)	.0329
HR 1 min recovery (bpm)	108.5 ± 15.8	110.4 ± 16.2	106.6 ± 15.4	ns
ΔHR 1 min recovery (bpm)	25.3 ± 9.9	28.4 ± 9.6	22.1 ± 9.3	.0058
MBP rest (mmHg)	103.0 ± 10.1	102.2 ± 8.6	103.7 ± 11.4	ns
MBP AT (mmHg)	137.5 ± 18.2	137.8 ± 16.9	137.2 ± 19.6	ns
MBP peak (mmHg)	147.9 ± 16.6	147.1 ± 16.8	148.6 ± 16.6	ns
RER peak	1.09 ± 0.06	1.10 ± 0.06	1.08 ± 0.06	ns
VO_2 rest (ml/min/kg)	4.2 ± 1.3	4.3 ± 1.2	4.1 ± 1.3	ns
VO_2 AT (ml/min/kg)	16.2 ± 4.8	17.7 ± 5.4	14.7 ± 3.6	.0077
VO_2 AT (%peakVO_2)	85.0 ± 8.5	84.6 ± 7.8	85.4 ± 9.2	ns
VO_2 peak (ml/min/kg)	19.0 ± 5.1	21.0 ± 5.7	17.1 ± 3.6	.0010
VO_2 rest (ml/min/kg eLBW)	5.9 ± 1.8	5.8 ± 1.7	6.0 ± 1.9	ns
VO_2 AT (ml/min/kg eLBW)	22.7 ± 5.8	24.2 ± 6.6	21.2 ± 5.5	.0293
VO_2 peak (ml/min/kg eLBW)	26.9 ± 6.0	28.7 ± 6.8	25.0 ± 4.3	.0076
VO_2 peak (%VO_{2max})	79.6 ± 16.1	81.7 ± 17.4	77.5 ± 14.7	ns
VE/VCO_2 slope	27.3 ± 3.8	27.8 ± 3.4	26.8 ± 4.2	ns
O_2 pulse peak (ml/bpm)	11.7 ± 2.6	11.9 ± 2.9	11.4 ± 2.4	ns
O_2 pulse peak (%max)	94.6 ± 16.6	94.1 ± 17.6	95.1 ± 15.7	ns
AV O_2 diff rest (ml/dl)	6.4 ± 2.2	6.4 ± 2.2	6.5 ± 2.4	ns
AV O_2 diff AT (ml/dl)	12.1 ± 3.2	12.1 ± 3.1	12.0 ± 3.5	ns
AV O_2 diff peak (ml/dl)	11.9 ± 3.1	11.9 ± 3.1	11.8 ± 3.2	ns
Resting and exercise echocardiography				
EDDi (mm/mq)	2.4 ± 0.2	2.4 ± 0.2	2.3 ± 0.2	.0228
EDVi (ml/m^2)	50.8 ± 11.5	53.1 ± 11.1	48.6 ± 11.6	ns
LVMi (g/m^2)	86.5 ± 17.4	88.2 ± 15.9	84.7 ± 18.8	ns
RWT	0.42 ± 0.05	0.41 ± 0.05	0.42 ± 0.05	ns
LAVi (ml/m^2)	25.0 ± 7.5	25.8 ± 7.7	24.2 ± 7.2	ns
SVi rest (ml/mq)	35.2 ± 7.6	35.9 ± 7.1	34.6 ± 8.2	ns
SVi at AT (ml/mq)	48.4 ± 11.1	49.6 ± 12.0	47.2 ± 10-0	ns
SVi peak (ml/m^2)	51.9 ± 11.7	53.4 ± 12.7	50.4 ± 10.5	ns
CO rest (L/min)	5.5 ± 1.3	5.4 ± 1.3	5.6 ± 1.3	ns
CO at AT (L/min)	11.4 ± 3.1	11.9 ± 3.5	10.9 ± 2.6	ns
CO peak (L/min)	13.7 ± 3.8	14.5 ± 4.3	13.0 ± 3.2	ns
LVEF rest (%)	59.1 ± 4.5	58.9 ± 4.7	59.3 ± 4.3	ns
LVEF at AT (%)	65.1 ± 5.4	64.6 ± 5.8	65.7 ± 4.9	ns
LVEF peak (%)	67.5 ± 5.9	67.2 ± 6.3	67.8 ± 5.4	ns
ΔEF (%)	8.4 ± 3.7	8.3 ± 4.0	8.5 ± .34	ns

(Continues)

TABLE 2 (Continued)

	All patients (n = 72)	Epicardial adipose tissue		
		≤ 5 mm (n = 36)	• > 5 mm (n = 36)	*P* value
GLS rest (%)	16.2 ± 2.6	16.0 ± 2.4	16.5 ± 2.9	ns
GLS 4 min (%)	18.2 ± 3.0	18.2 ± 3.1	18.2 ± 2.9	ns
ΔGLS (%)	2.0 ± 1.4	2.1 ± 1.7	1.8 ± 1.1	ns
S′ mean rest (cm/s)	9.3 ± 1.8	9.2 ± 1.8	9.3 ± 1.7	ns
S′ mean AT (cm/s)	13.0 ± 2.5	13.3 ± 2.7	12.7 ± 2.2	ns
S′ mean peak (cm/s)	14.4 ± 2.9	15.0 ± 3.3	13.9 ± 2.5	ns
ΔS′ mean (cm/sec)	5.1 ± 2.2	5.8 ± 2.5	4.6 ± 1.6	.0268
E/A rest	0.90 ± 0.22	0.96 ± 0.04	0.83 ± 0.03	.0083
E/e′ rest (cm/s)	8.3 ± 2.3	8.7 ± 2.1	8.6 ± 2.5	ns
E/e′ peak (cm/s)	8.5 ± 1.9	8.2 ± 1.7	8.7 ± 2.2	ns
SVR rest (dyne[a]s/cm)	1577 ± 368	1601 ± 389	1554 ± 349	ns
SVR at AT (dyne[a]s/cm)	1018 ± 262	996 ± 283	1042 ± 241	ns
SVR peak (dyne[a]s/cm)	914 ± 228	873 ± 252	955 ± 196	ns
CPO rest (W)	1.3 ± 0.3	1.2 ± 0.3	1.3 ± 0.4	ns
CPO peak (W)	4.6 ± 1.6	4.8 ± 1.7	4.3 ± 1.4	ns
ΔCPO (%)	2.7 ± 1.2	3.0 ± 1.2	2.5 ± 1.0	.0405
Plasma biomarkers				
hsCRP (mg/dl)	0.291 ± 0.485	0.130 (0.058-0.235)	0.176 (0.081-0.481)	ns
TnHS (ng/ml)	11.2 (6.0-13.8)	9.6 (6.0-16.4)	8.7 (6.6-15.9)	ns
Pro-ADM (nmol/L)	0.12 ± 0.13	0.13 ± 0.11	0.11 ± 0.15	ns
NT-PRO3 (ng/ml)	6.10 (4.67-7.91)	6.10 (4.46-6.99)	6.16 (4.69-9.87)	ns
TNFα (pg/ml)	0.69 (0.59-0.94)	0.73 (0.60-0.99)	0.57 (0.49-0.95)	ns
BNP (pg/ml)	14 (10-31)	10 (10-24)	20 (10-36)	.0102
NT-proBNP (pg/ml)	41 (28-116)	31 (26-139)	64 (29-165)	.0405

Abbreviations: Δ, difference from rest to peak exercise; AT, anaerobic threshold; AV O_2 diff, artero-venous oxygen difference or peripheral extraction; BNP, brain natriuretic peptide; CO, cardiac output; CPO, cardiac power output; E/A, transmitral early to atrial diastolic waves; E/e′, E wave to mean (medial and lateral) early diastolic movement of mitral annulus with tissue Doppler; EAT, epicardial adipose tissue; EDDi, end-diastolic diameter index; EDVi, end-diastolic volume index; EF, ejection fraction; eLBW, estimated lean body weight; GLS, global longitudinal strain; HR, heart rate; hsCRP, high-sensitivity C-reactive protein; LAVi, left atrial volume index; LVEF, left ventricular ejection fraction; LVMi, left ventricular mass index; MBP, mean blood pressure; NT-PRO3, N-terminal pro-collagen 3; NT-proBNP, N-terminal pro-brain natriuretic peptide; Pro-ADM, proadrenomedullin; RER, respiratory exchange ratio; RWT, relative wall thickness; S′, mean (medial and lateral) systolic movement of mitral annulus with tissue Doppler; SVi, stroke volume index; SVR, systemic vascular resistance; TNFa, tumour-necrosis factor alpha; TnHS, high-sensitivity troponin T; VE/VCO_2, ventilation/carbon dioxide output ratio (ventilatory efficiency); VO_2, oxygen uptake.

[a]The study population is reported as a whole and divided into two groups based on EAT thickness above or below the median (5 mm). *P* values were calculated with a Student *t*-test for paired data and chi-squared test for nominal variables, and are reported as 'ns' if non-significant.

average e′ and average E/e′ ratio values, which is in line with other studies[4,28]; all diastolic variables remained within normality throughout the CPET. The isolated E/A impairment at rest might be an early effect of the smaller LV dimensions associated with increased EAT, because the other variables are less dependent on volumetric and preload conditions: the constrained LV is stiffer and the LA contribution to diastolic ventricular filling is comparatively higher.

Subjects with higher EAT thickness achieved a lower workload and worse cardiopulmonary fitness, despite all patients completing a maximal CPET with similar duration of exercise, as per the protocol. Specifically, individuals with a higher EAT thickness reached an early anaerobic threshold and a lower VO_{2peak} (invariably expressed as both ml/min/kg of body weight and ml/min/kg of estimated lean body weight), with mean values below 80% of the maximal theoretic (expected) VO_2, which is the threshold for effort intolerance, while displaying a reduced VO_2/work slope. Also, an EAT thickness of more than 5 mm was associated with impaired systolic reserve (as expressed through a reduced increase in TDI-derived S′ and in CPO from rest to peak exercise), despite no influence on resting LV-GLS. This is in line with previous data in a similar population showing that EAT thickness is related to resting S′ values.[29] The lack of difference in LV-GLS might depend on either the study exclusion criteria (LV-GLS < 16% is a minor diagnostic criterion for the diagnosis of HFpEF[1]), or the lack of a measurement of GLS at peak exercise

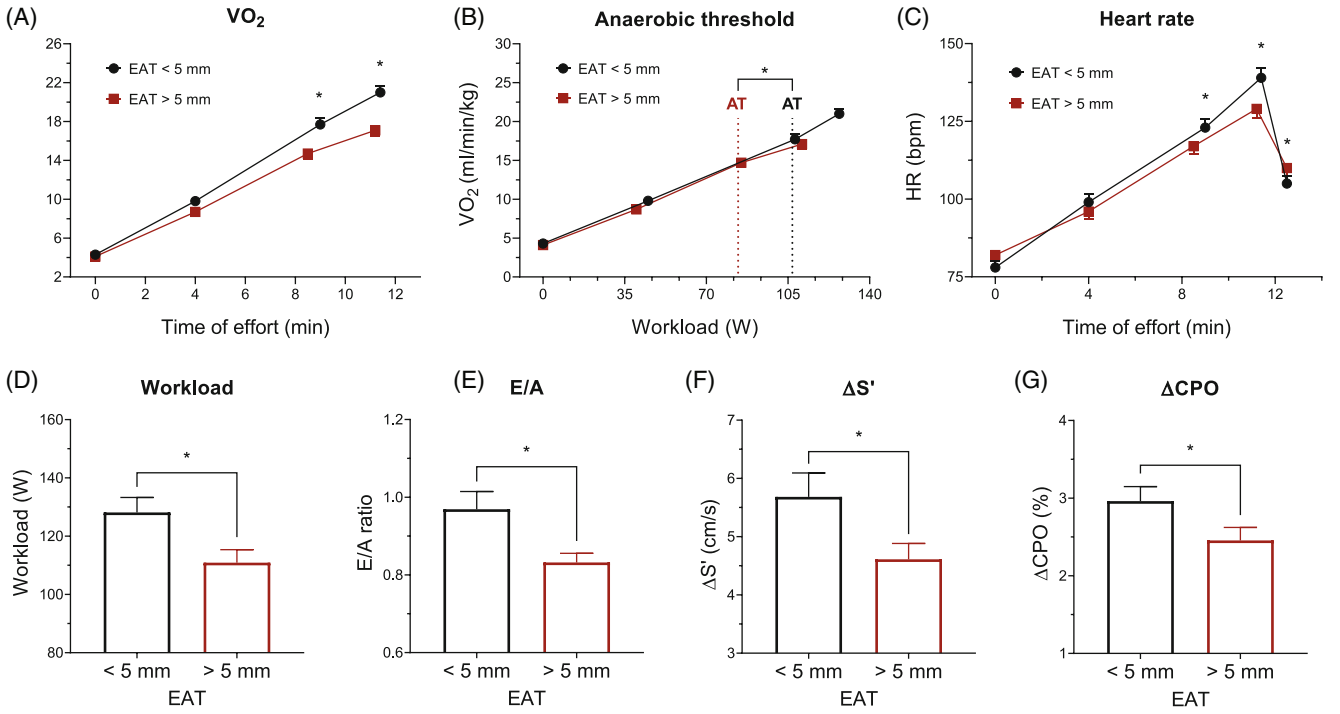

FIGURE 2 Impact of epicardial adipose tissue (EAT) thickness on cardiopulmonary exercise test and exercise echocardiography. The main results of the cardiopulmonary exercise test and exercise echocardiography are reported. Patients with lower EAT thickness are displayed in black and the ones with higher thickness are displayed in red. Mean values and error are reported; statistically significant differences between the two groups are indicated by an asterisk (*). A, Oxygen uptake (VO_2) versus time of effort. B, VO_2 with anaerobic threshold vs workload. C, Heart rate (HR) dynamics versus time of effort. D, Peak achieved workload. E, E-to-A wave ratio at rest. F, Increase from rest to peak exercise in systolic movement of mitral annulus at tissue Doppler. G, Increase from rest to peak exercise in cardiac power output (CPO)

because of technical limitations during high HR. Our data extend to T2D with normal heart function what has been reported in both T2D and HF[30] and in obese subjects with HFpEF.[31]

Increased EAT thickness is also related to chronotropic insufficiency with lower peak HR and altered HR recovery in the first minute of unloaded pedalling after the end of the exercise, which is a known negative prognostic factor. The tight association with autonomic derangements, despite the absence of a definite diagnosis of cardiac autonomic neuropathy (at rest), advocates a negative effect of EAT on cardiac sympatho-vagal balance during exercise, which is the earliest sign of autonomic dysfunction and a known determinant of impaired aerobic capacity. Of note, EAT thickness is an important risk factor for recurrence of LA fibrillation after catheter ablation.[32] An influence on autonomic balance might partly justify the reduced workload and oxygen uptake, but weakly explains the associated contractility impairment.

Our observation of a positive linear relationship between natriuretic peptides and EAT thickness and their different values in the two subgroups support this point as well. To our knowledge, this is the first report of a correlation between EAT thickness and natriuretic peptides in T2D, which came quite unexpectedly, because EAT thickness is greater in obese subjects, who usually display lower values of natriuretic peptides.[33] Nonetheless, a direct relationship between natriuretic peptides and EAT thickness has been found in stable coronary artery disease, during acute stroke,[34] and inconsistently in HFpEF.[8,35,36] Although inflammation has been previously suggested as a possible mediator of EAT effects on the myocardium,[6] our results do not confirm this.

Considering the frequent and significant limitations to exercise capacity found in T2D subjects,[37] the compromised systolic reserve and HR adjustments paired with normal variables of ventilation, metabolism and peripheral oxygen extraction suggest that hypertrophied/dysfunctional EAT acts through a direct effect on the myocardium, and specifically on both autonomic control and contractility reserve. This hypothesis is further corroborated by the observation of the linear correlation between natriuretic peptides, HR kinetics and EAT thickness, as well as the independent association of EAT with VO_{2peak}. Of note, the main alterations that we found in the subgroup with an EAT thickness of more than 5 mm are among the key characteristics of HFpEF, namely: effort intolerance, chronotropic insufficiency,[1] reduced systolic reserve, impaired cardiac power output,[38] increased natriuretic peptides, cardiac chamber dimensions and geometry,[1] and increased EAT thickness itself,[4] despite no patient among our study population meeting the diagnostic criteria for HFpEF.[1] EAT is known to be related to VO_{2peak} in overt HFpEF together with similar, but more pronounced, haemodynamic derangements both at rest and during exercise, and especially a positive diastolic stress test with increased right-sided filling pressures.[39] Hence, one might infer that stress-induced diastolic dysfunction, increased heart chamber pressures and frankly impaired LV-GLS are a more

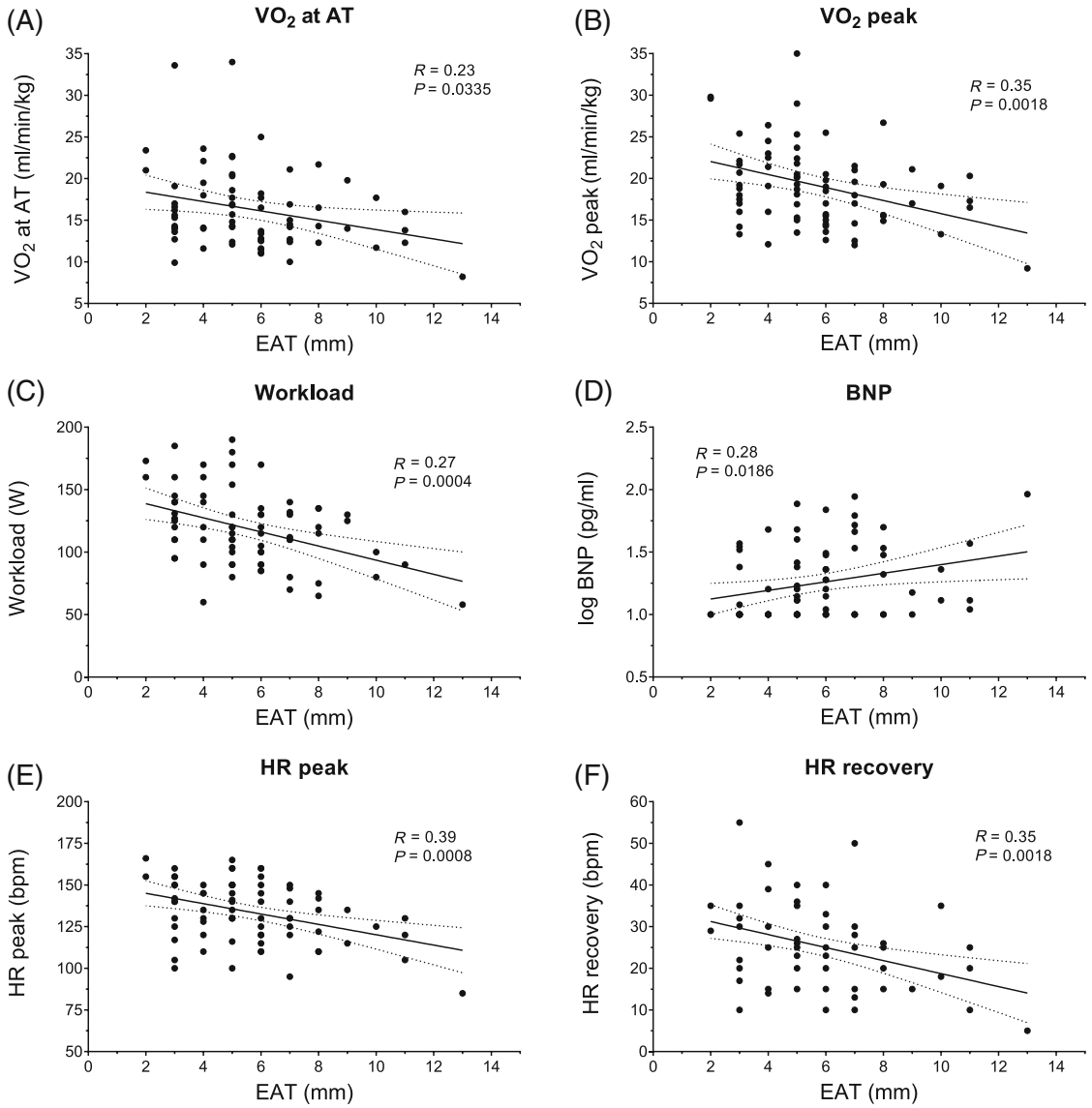

FIGURE 3 Linear regression analysis. Epicardial adipose tissue (EAT) thickness linearly correlated with oxygen uptake (VO_2) at both A, Anaerobic threshold (AT), and B, Peak exercise; with C, Workload, D, Brain natriuretic peptides (BNP), and heart rate (HR) at both E, Peak exercise and F, During the first minute of recovery

advanced feature of myocardial impairment that marks the progression to effort intolerance and eventually to overt HFpEF. In this interpretation, the iCPET phenotype of T2D patients with increased EAT thickness can be regarded as intermediate between uncomplicated T2D and overt HFpEF, therefore possibly identifying a subgroup of patients with stage B HF at increased risk of developing symptomatic HF. The biological plausibility had already been recognized, because EAT has been proposed to have a causal role in HF progression.[40] Moreover, considering the impressive protective effects of sodium-glucose co-transporter-2 inhibitors on HF development and hospitalizations in this population,[41] the observation that this class of drugs early and significantly reduces EAT thickness in T2D without HF[42] might further support our hypothesis.

Like other visceral adipose tissues, EAT is subjected to diabetes-related maladaptive biology, which is characterized by a protective storage of excess energy substrates (mainly glucose) that eventually becomes maladaptive leading to adipocyte hypertrophy, failure to store triglycerides, increased lipolysis and inflammation.[43,44] Sharing the microcirculation, the spatial and functional proximity of EAT to the coronary arteries, conduction system and LA and ventricular myocardium, might justify the link between EAT and both systo-diastolic functions and autonomic dysregulations through a combination of mechanical, vasocrine and paracrine interactions. In T2D, EAT displays a specific dysfunctional phenotype[45]: it releases excess fatty acids in the coronary circulation not entirely used by cardiomyocytes for energy production leading to myocardial steatosis, which in turn impairs myocytes' contractile functions[46] and promotes fetal gene expression that ultimately leads to adverse LV remodelling and fibrosis.[47] Additionally, hypertrophied EAT can also exert mechanic interference (i.e. structural sustain and reduced attrition) on cardiac

functions: in obese HFpEF patients, EAT hypertrophy imposes mechanical stress through pericardial restrain, causing higher intracardiac pressures.[31,48] Our report of smaller indexed LV cavity sustains the mechanical stress hypothesis, albeit to a lesser extent than in overt HFpEF, intracardiac pressures being within normal range in our population. Other pathophysiological mechanisms have been proposed, namely, adrenergic downregulation, thermogenic dysfunction, oxidative stress and paracrine/endocrine modulation (secretion of angiotensin, adipokine synthesis), but has never been confirmed in T2D without heart disease.[49] The normal values of markers of myocyte damage and extracellular matrix remodelling further sustain the direct effect of dysfunctional EAT on the myocardium through metabolic rather than structural interference.

This work presents some limitations. Because of the cross-sectional design, we are unable to infer causality between EAT thickness and the observed cardiopulmonary and haemodynamic derangements and cannot rule out unmeasured or residual confounding as a reason for the observed findings. Potential confounders are an uneven distribution of EAT that was shown for HFrEF,[50] but not in T2D, and impaired coronary flow, which could not be measured by positron emission tomography because of financial and ethical committee limitations (nonetheless, coronary artery disease was excluded in all patients by a maximal exercise test). By the statistical correction for the main factors known to impact on cardiopulmonary fitness, we have attempted to account for these potential caveats. This was a pilot study designed to explore a broad range of variables that may be affected by EAT. As such, our study had multiple exploratory outcomes but no primary objective (or sample size calculation), which warrants caution, particularly in the interpretation of negative findings. Similar caution must be advised for the interpretation of borderline significance because of multiple testing (ΔCPO and NT-proBNP).

AUTHOR CONTRIBUTIONS

LN ideated the research hypothesis, performed patient screening, baseline metabolic, vascular, neurological, and clinical evaluation, created the database, performed the statistical analysis, wrote the manuscript, ideated and created tables and figures. NRP ideated the research hypothesis, performed echocardigoraphy and exercise cardiopulmonary tests, gave a substantial contribution to the interpretation of data, helped writing the manuscript. MC, DT performed patient screening, statistical analysis, and gave a major contribution in the rendering of tables and figure. SB performed biochemical and biomarker analysis, kept and stored blood samples. AN ideated and supervised the study, gave key contribution in the analysis and interpretation of data.

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CONFLICT OF INTEREST

No author has conflict of interest to declare with respect to the current study.

PEER REVIEW

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DATA AVAILABILITY STATEMENT

NA

ORCID

Lorenzo Nesti https://orcid.org/0000-0002-0560-6496
Martina Chiriacò https://orcid.org/0000-0003-0174-4549
Domenico Trico https://orcid.org/0000-0002-7633-1346

REFERENCES

1. Pieske B, Tschope C, de Boer RA, et al. How to diagnose heart failure with preserved ejection fraction: the HFA-PEFF diagnostic algorithm: a consensus recommendation from the Heart Failure Association (HFA) of the European Society of Cardiology (ESC). *Eur Heart J*. 2019;40(40):3297-3317.
2. Salvatore T, Galiero R, Caturano A, et al. Dysregulated epicardial adipose tissue as a risk factor and potential therapeutic target of heart failure with preserved ejection fraction in diabetes. *Biomolecules*. 2022;12(2):176.
3. Iacobellis G, Corradi D, Sharma AM. Epicardial adipose tissue: anatomic, biomolecular and clinical relationships with the heart. *Nat Clin Pract Cardiovasc Med*. 2005;2(10):536-543.
4. Christensen RH, Hansen CS, von Scholten BJ, et al. Epicardial and pericardial adipose tissues are associated with reduced diastolic and systolic function in type 2 diabetes. *Diabetes Obes Metab*. 2019;21(8):2006-2011.
5. van Woerden G, Gorter TM, Westenbrink BD, Willems TP, van Veldhuisen DJ, Rienstra M. Epicardial fat in heart failure patients with mid-range and preserved ejection fraction. *Eur J Heart Fail*. 2018;20(11):1559-1566.
6. Vyas V, Blythe H, Wood EG, et al. Obesity and diabetes are major risk factors for epicardial adipose tissue inflammation. *JCI Insight*. 2021;6(16):e145495.
7. Greulich S, Maxhera B, Vandenplas G, et al. Secretory products from epicardial adipose tissue of patients with type 2 diabetes mellitus induce cardiomyocyte dysfunction. *Circulation*. 2012;126(19):2324-2334.
8. Pugliese NR, Paneni F, Mazzola M, et al. Impact of epicardial adipose tissue on cardiovascular haemodynamics, metabolic profile, and prognosis in heart failure. *Eur J Heart Fail*. 2021;23(11):1858-1871.
9. Pugliese NR, Pieroni A, De Biase N, et al. Impact of diabetes on cardiopulmonary function: the added value of a combined cardiopulmonary and echocardiography stress test. *Heart Fail Rev*. 2021. doi: 10.1007/s10741-021-10194-7
10. American Diabetes Association. 2. Classification and diagnosis of diabetes: standards of medical care in diabetes-2020. *Diabetes Care*. 2020;43(Suppl 1):S14-S31.
11. McDonagh TA, Metra M, Adamo M, et al. 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J*. 2021;42(36):3599-3726.
12. Yu S, Visvanathan T, Field J, et al. Lean body mass: the development and validation of prediction equations in healthy adults. *BMC Pharmacol Toxicol*. 2013;14:53.
13. Trico D, Nesti L, Frascerra S, Baldi S, Mengozzi A, Natali A. A protein/lipid preload attenuates glucose-induced endothelial dysfunction in individuals with abnormal glucose tolerance. *Nutrients*. 2020;12(7):2053.
14. Dimitropoulos G, Tahrani AA, Stevens MJ. Cardiac autonomic neuropathy in patients with diabetes mellitus. *World J Diabetes*. 2014;5(1):17-39.

15. American Thoracic Society, American College of Chest Physicians. ATS/ACCP statement on cardiopulmonary exercise testing. *Am J Respir Crit Care Med*. 2003;167(2):211-277.
16. Nesti L, Pugliese NR, Sciuto P, et al. Mechanisms of reduced peak oxygen consumption in subjects with uncomplicated type 2 diabetes. *Cardiovasc Diabetol*. 2021;20(1):124.
17. Brubaker PH, Kitzman DW. Chronotropic incompetence: causes, consequences, and management. *Circulation*. 2011;123(9):1010-1020.
18. Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging*. 2015;16(3):233-270.
19. Dini FL. Assessment of cardiac dynamics during stress echocardiography by the peak power output-to-left ventricular mass ratio. *Future Cardiol*. 2011;7(3):347-356.
20. Shimiaie J, Sherez J, Aviram G, et al. Determinants of effort intolerance in patients with heart failure: combined echocardiography and cardiopulmonary stress protocol. *JACC Heart Fail*. 2015;3(10):803-814.
21. Iacobellis G, Assael F, Ribaudo MC, et al. Epicardial fat from echocardiography: a new method for visceral adipose tissue prediction. *Obes Res*. 2003;11(2):304-310.
22. Marwick TH, Gimelli A, Plein S, et al. Multimodality imaging approach to left ventricular dysfunction in diabetes: an expert consensus document from the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging*. 2022;23(2):e62-e84.
23. Graeff DB, Foppa M, Pires JC, et al. Epicardial fat thickness: distribution and association with diabetes mellitus, hypertension and the metabolic syndrome in the ELSA-Brasil study. *Int J Cardiovasc Imaging*. 2016;32(4):563-572.
24. Argan O, Avci E, Yildirim T, Safak O. Epicardial adipose tissue is a predictor of ascending aortic dilatation in hypertensive patients, but not paracardial adipose tissue. *BMC Cardiovasc Disord*. 2020;20(1):142.
25. Doesch C, Haghi D, Fluchter S, et al. Epicardial adipose tissue in patients with heart failure. *J Cardiovasc Magn Reson*. 2010;12:40.
26. Doesch C, Haghi D, Suselbeck T, Schoenberg SO, Borggrefe M, Papavassiliu T. Impact of functional, morphological and clinical parameters on epicardial adipose tissue in patients with coronary artery disease. *Circ J*. 2012;76(10):2426-2434.
27. Shah RV, Anderson A, Ding J, et al. Pericardial, but not hepatic, fat by CT is associated with CV outcomes and structure: the multi-ethnic study of atherosclerosis. *JACC Cardiovasc Imaging*. 2017;10(9):1016-1027.
28. Nerlekar N, Muthalaly RG, Wong N, et al. Association of volumetric epicardial adipose tissue quantification and cardiac structure and function. *J Am Heart Assoc*. 2018;7(23):e009975.
29. Watanabe K, Kishino T, Sano J, et al. Relationship between epicardial adipose tissue thickness and early impairment of left ventricular systolic function in patients with preserved ejection fraction. *Heart Vessels*. 2016;31(6):1010-1015.
30. Sugita Y, Ito K, Sakurai S, Sakai S, Kuno S. Epicardial adipose tissue is tightly associated with exercise intolerance in patients with type 2 diabetes mellitus with asymptomatic left ventricular structural and functional abnormalities. *J Diabetes Complications*. 2020;34(5):107552.
31. Koepp KE, Obokata M, Reddy YNV, Olson TP, Borlaug BA. Hemodynamic and functional impact of epicardial adipose tissue in heart failure with preserved ejection fraction. *JACC Heart Fail*. 2020;8(8):657-666.
32. Zhou M, Wang H, Chen J, Zhao L. Epicardial adipose tissue and atrial fibrillation: possible mechanisms, potential therapies, and future directions. *Pacing Clin Electrophysiol*. 2020;43(1):133-145.
33. Jordan J, Birkenfeld AL, Melander O, Moro C. Natriuretic peptides in cardiovascular and metabolic crosstalk: implications for hypertension management. *Hypertension*. 2018;72(2):270-276.
34. Altun I, Unal Y, Basaran O, et al. Increased epicardial fat thickness correlates with aortic stiffness and N-terminal pro-brain natriuretic peptide levels in acute ischemic stroke patients. *Tex Heart Inst J*. 2016;43(3):220-226.
35. Selvaraj S, Kim J, Ansari BA, et al. Body composition, natriuretic peptides, and adverse outcomes in heart failure with preserved and reduced ejection fraction. *JACC Cardiovasc Imaging*. 2021;14(1):203-215.
36. Nyawo TA, Dludla PV, Mazibuko-Mbeje SE, et al. A systematic review exploring the significance of measuring epicardial fat thickness in correlation to B-type natriuretic peptide levels as prognostic and diagnostic markers in patients with or at risk of heart failure. *Heart Fail Rev*. 2022;27(2):665-675.
37. Nesti L, Pugliese NR, Sciuto P, Natali A. Type 2 diabetes and reduced exercise tolerance: a review of the literature through an integrated physiology approach. *Cardiovasc Diabetol*. 2020;19(1):134.
38. Harada T, Yamaguchi M, Omote K, et al. Cardiac power output is independently and incrementally associated with adverse outcomes in heart failure with preserved ejection fraction. *Circ Cardiovasc Imaging*. 2022;15(2):e013495.
39. Gorter TM, van Woerden G, Rienstra M, et al. Epicardial adipose tissue and invasive hemodynamics in heart failure with preserved ejection fraction. *JACC Heart Fail*. 2020;8(8):667-676.
40. Christensen RH, von Scholten BJ, Lehrskov LL, Rossing P, Jorgensen PG. Epicardial adipose tissue: an emerging biomarker of cardiovascular complications in type 2 diabetes? *Ther Adv Endocrinol Metab*. 2020;11:2042018820928824.
41. Natali A, Nesti L, Trico D, Ferrannini E. Effects of GLP-1 receptor agonists and SGLT-2 inhibitors on cardiac structure and function: a narrative review of clinical evidence. *Cardiovasc Diabetol*. 2021;20(1):196.
42. Sato T, Aizawa Y, Yuasa S, et al. The effect of dapagliflozin treatment on epicardial adipose tissue volume. *Cardiovasc Diabetol*. 2018;17(1):6.
43. Rabkin SW. The relationship between epicardial fat and indices of obesity and the metabolic syndrome: a systematic review and meta-analysis. *Metab Syndr Relat Disord*. 2014;12(1):31-42.
44. McAninch EA, Fonseca TL, Poggioli R, et al. Epicardial adipose tissue has a unique transcriptome modified in severe coronary artery disease. *Obesity*. 2015;23(6):1267-1278.
45. Nosalski R, Alsheikh EO, Guzik TJ. Diabetes enhances epicardial fat dysfunction. *Pol Arch Intern Med*. 2019;129(11):733-734.
46. Yamaguchi Y, Cavallero S, Patterson M, et al. Adipogenesis and epicardial adipose tissue: a novel fate of the epicardium induced by mesenchymal transformation and PPARgamma activation. *Proc Natl Acad Sci U S A*. 2015;112(7):2070-2075.
47. Han Y, Ferrari VA. Fatty heart and subclinical left ventricular dysfunction: rediscovery of a pathological metabolic process: with a twist. *Circ Cardiovasc Imaging*. 2013;6(5):614-616.
48. Elsanhoury A, Nelki V, Kelle S, Van Linthout S, Tschope C. Epicardial fat expansion in diabetic and obese patients with heart failure and preserved ejection fraction-a specific HFpEF phenotype. *Front Cardiovasc Med*. 2021;8:720690.
49. Gruzdeva O, Borodkina D, Uchasova E, Dyleva Y, Barbarash O. Localization of fat depots and cardiovascular risk. *Lipids Health Dis*. 2018;17(1):218.
50. van Woerden G, van Veldhuisen DJ, Gorter TM, 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):987-993.

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