

Associations of region-specific visceral adiposity with subclinical atrial dysfunction and outcomes of heart failure

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Abstract

Aims Excessive visceral adiposity (VAT) plays an essential role in metabolic derangements with those close to heart further mediates myocardial homeostasis. The disparate biological links between region-specific VAT and cardiometabolic profiles as mediators influencing atrial kinetics remain unexplored.

Methods and results Among 1326 asymptomatic individuals, region-specific VAT including peri-aortic root fat (PARF) and total pericardial fat (PCF) of cardiac region, together with thoracic peri-aortic adipose tissue (TAT), was assessed using multiple-detector computed tomography. VAT measures were related to functional left atrial (LA) metrics assessed by speckle-tracking algorithm and clinical outcomes of atrial fibrillation (AF) and heart failure (HF). Multivariate linear regression models incorporating body fat, metabolic syndrome, and E/TDI-e' consistently demonstrated independent associations of larger PARF/PCF with peak atrial longitudinal systolic strain (PALS) reduction, higher LA stiffness, and worsened strain rate components; instead, TAT was independently associated with cardiometabolic profiles. PARF rather than PCF or TAT conferred independent prognostic values for incident AF/HF by multivariate Cox regression (adjusted hazard ratio: 1.56, 95% confidence interval: 1.17–2.08, $P = 0.002$) during a median of 1790 days (interquartile range: 25th to 75th: 1440–1927 days) of follow-up, with subjects categorized into worst PALS and largest VAT tertiles demonstrating highest events (all log-rank $P < 0.001$). Mediation analysis showed that higher triglyceride and lower high-density lipoproteins may serve as intermediary factors for effects between VAT and LA functional metrics, with lesser role by glucose level.

Conclusions Visceral adiposity surrounding atrial region was tightly associated with subclinical atrial dysfunction and incident AF or HF beyond metabolic factors. Instead, peri-aortic adiposity may mediate their toxic effects mainly through circulating cardiometabolic profiles.

Keywords Left atrial strain; Strain rate; Mediator; Cardiometabolic; Computed tomography; Visceral fat

Received: 16 October 2019; Revised: 30 March 2020; Accepted: 27 April 2020

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Condensed abstract: Among 1326 asymptomatic individuals, visceral adiposity (VAT) by multiple-detector computed tomography was independently associated with peak atrial longitudinal strain and strain rate measures beyond body fat composition and left ventricular filling (E/TDI-e'). Pericardial fat and peri-aortic root fat in anatomic proximity to cardiac or left atrial (LA) region demonstrated independent links with atrial kinetics, with attenuated associations observed in thoracic peri-aortic fat. Mediator analysis showed that triglycerides, high-density lipoproteins, and fasting blood sugar played intermediary roles between VAT and LA metrics. During a median of 1790 days follow-up, subjects with greater VAT and worse LA strain experienced markedly higher clinical episodes of heart failure and atrial fibrillation.

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Introduction

Total body adiposity depots offer biological survival advantages including energy reserve to fuel essential physiological functions, while also playing several pivotal biochemical roles, including hormone production.^{1,2} Excessive energy consumption, however, is harmful and has led to unhealthy obese, insulin resistance, or clustered manifestations of metabolic derangements known as 'metabolic syndrome' (MetS).³ Recent evidence has shown that visceral adiposity (VAT), especially surrounding the heart, may contribute independently to adverse biological effects on the myocardium through chemotactic, pro-inflammatory cytokines (e.g. interleukin 6) and cardiometabolic factors in unhealthy obesity or under metabolic stress, leading to 'cardiac steatosis' and diabetic cardiomyopathy.^{4–7} Except for dysglycaemic signalling, an alternative pathophysiological link between excessive VAT and myocardial damage has recently been proposed from high levels of circulating free fatty acids and dysregulated metabolic profiles [such as high-density lipoprotein (HDL) or triglyceride (TG)⁴] in mediating excessive myocardial TG accumulation and lipotoxicity.^{8,9}

More recently, phenotypic obesity has been shown to be associated with mechanical atrial dysfunction in a pre-clinical stage^{10,11} and higher risk for incident atrial fibrillation (AF).^{12,13} As a thin-walled structure, the atrium is particularly prone to pathological inflammatory processes or elevated ventricular filling pressure acting as a 'barometer', which serves as a clinical hallmark in preserved ejection fraction heart failure (HF) (HFpEF) and AF.¹³ Owing to asymmetrical atrial structure and geometry, quantitative functional metrics of the left atrium utilizing speckle-tracking technique can be more sensitive, relatively load-independent¹⁴ and may better characterize mechanical LA functions at a pre-clinical stage prior to overt chamber dilation with improved prognostic values.¹⁵

Despite these known associations, little is known regarding the potential disparate pathological effects and intermediary metabolic process of region-specific VAT on atrial kinetics using deformational indices. Therefore, we aimed to investigate these associations and further examined their prognostic values in a large, asymptomatic population.

Methods

Study subjects

The study subjects comprised a subpopulation from a previously published asymptomatic population who underwent annual cardiovascular health surveys (from June 2009 to December 2012).¹⁶ A total of the 4848 participants were eligible for a comprehensive physical examination, 12-lead

complete electrocardiogram (ECG), biochemical analysis, comprehensive transthoracic echocardiography (equipped with tissue Doppler imaging/speckle-tracking technique), and multiple-detector computed tomography (MDCT) for coronary calcium screening. Individuals currently using anti-lipid medications (statins or fibrate) were excluded to eliminate possible interference with mediator analysis. Comparisons of baseline characteristics of study subjects included and not included in the current study are presented in Supporting Information, *Table S1* (final $n = 1326$). A detailed, structured questionnaire about subjective symptoms was administered to all study participants. Hypertension was defined by a mean systolic blood pressure (SBP) ≥ 140 mmHg and/or a mean diastolic blood pressure ≥ 90 mmHg measured three times consecutively from the brachial artery. Diabetes diagnosis followed the 2011 Standards of Medical Care in Diabetes guidelines developed by the American Diabetes Association, or known diabetes history, or the current use of diabetes medication. Patients with cardiovascular disease (CVD) included known coronary artery disease or cerebrovascular disease. This study was approved by the ethics committee of the MacKay Memorial Hospital (No. 14MMHIS202) in compliance with the Declaration of Helsinki.

Conventional echocardiography and myocardial atrial deformation

Echocardiography was performed using a 2–4 MHz transducer following the recommendations of the American Society of Echocardiography and included wall thickness, left ventricular (LV) mass, with LA/LV volume (maximum and minimum) assessed by a modified biplane Simpson's method. The LA emptying fraction (LAEF) was defined as follows: $LAEF = 100 \times (\text{maximum LA volume} - \text{minimum LA volume}) / \text{maximum LA volume}$. Haemodynamic Doppler of early (E) and late mitral inflow (A), deceleration time, and isovolumic relaxation time values were obtained. Tissue Doppler information defined LV systolic (TDI-s') and early diastolic (TDI-e') myocardial velocities were also determined and averaged from LV septal and lateral basal segments. The deformational metrics of the left atrium were further analysed according to a previous published protocol utilizing EchoPAC software (version 10.8, GE Vingmed Ultrasound, Norway) by an experienced technician blinded to clinical information.¹⁶ Based on a built-in algorithm, the peak atrial longitudinal systolic strain (PALS) and strain rate (SR) curves for each LA segment were automatically generated from the cardiac apex 4CH and 2CH views after manual tracing using R–R gating method as our previous work.¹⁶ Global peak atrial longitudinal systolic strain (PALS) and LA SR curves from three distinct phases, systolic (SRs) during the reservoir phase, early diastolic (SRe) during the conduit phase, and late diastolic (SRa) as atrial contractile/booster pump function, were assessed. All representative LA deformational indices

were derived from averaged 4CH and 2CH values. A high absolute value of the PALS or SR measures indicated better myocardial atrial deformation. The reproducibility of 50 random subjects showed coefficient of variance of 6.4%, 5.6%, 4.4%, and 5.8% between raters (inter-observer variability) of PALS, LA reservoir, conduit, and contractile and 4.8%, 4.4%, 4.0%, and 4.6% within the same rater (intra-observer variability), respectively.¹⁶

Three-dimensional quantitative assessment of region-specific visceral adiposity by multiple-detector computed tomography

All VAT measures, including those surrounding visceral heart organs [peri-aortic root fat (PARF) and pericardial fat (PCF)] classified as cardiac region, and those surrounding thoracic peri-aortic region classified as non-cardiac region, were quantified after three-dimensional reconstruction using cardiac computed tomography by dedicated workstation (Aquarius 3D Workstation, TeraRecon, San Mateo, CA, USA) with high spatial resolution. Scans were performed using a 16-slice MDCT scanner (Sensation 16; Siemens Medical Solutions, Forchheim, Germany) with 16 × 0.75 mm collimation, rotation time of 420 ms, and tube voltage of 120 kV. PCF was defined as adipose tissue located within the pericardial sac. Thoracic peri-aortic adipose tissue (TAT) was defined as adipose tissue surrounding the thoracic aorta extending 67.5 mm caudally from the level of the bifurcation of pulmonary arteries. In addition, PARF was defined as adipose tissue within the pericardial sac near aortic root region extending cranially 24 mm from the left main coronary artery as previously validated and published^{6,17} (Figure 1).

Assessment of total body composition

Total body fat (TBF) was determined utilizing a bioelectrical impedance method measured based on foot-to-foot impedance assessed through a Tanita-305 Body-Fat Analyser (Tanita Corp, Tokyo, Japan). The assessment of body fat composition enables objective quantification of body fat percentage and provides segmental and total body measure of fat, fat-free, and water composition presented as fractions/percentage. In this study, TBF was defined as follows: $100 \times (\text{body weight [in kg]} \times \text{body fat composition in percentage [\%]})$ as a continuous variable.

Biochemical laboratory analysis

All biochemical data were collected from venipuncture and analysed using a Hitachi 7170 Automatic Analyser (Hitachi Corp. Hitachinaka Ibaraki, Japan), with blood glucose levels

[before and after a meal (hexokinase method), glycosylated haemoglobin], complete blood lipid profiling (total cholesterol, TG, HDL, and low-density lipoprotein), and kidney function tests (creatinine) that were determined by homogenous enzymatic colorimetric assay. Systemic inflammation marker high-sensitivity C-reactive protein (hs-CRP) was determined using a highly sensitive, latex particle-enhanced immunoassay (Elecsys 2010, Roche, Mannheim, Germany). Insulin was excluded from comparison because of limited data ($n = 710$).

Definition of metabolic syndrome

We defined subjects with MetS as having at least three of the following criteria: (i) abnormal high BP: SBP ≥ 130 mmHg or diastolic BP ≥ 85 mmHg or known hypertension; (ii) sex-stratified central obesity (waist circumference ≥ 90 cm for men or ≥ 80 cm for women; (iii) TG ≥ 150 mg/dL; (iv) HDL < 40 mg/dL in men or < 50 mg/dL in women; and (v) abnormal blood sugar level defined by fasting plasma sugar ≥ 100 mg/dL or known diabetes history.

Endpoints

We specified two primary endpoints of interest as a composite endpoint: (i) new-onset AF and (ii) incidental HF hospitalization adjudicated by cardiologists. Body surface ECG was obtained and new onset AF was considered to present whenever a new diagnosis code of AF (ICD code: 427.31) or atrial flutter (ICD code: 427.32) was present during unscheduled outpatient visits or during sequential regular follow-up (biennially).

Statistical analysis

Continuous variables were expressed as mean \pm standard deviation or median and interquartile range provided where necessary, with categorical variables expressed as percentage or ratio and compared by χ^2 . Relevant demographic clinical data and echocardiography parameters as continuous variables were presented across VAT tertiles using Cuzick's non-parametric trend test, with categorical variables examined using the chi-square test (Table 1). Univariate and multivariate linear regression models were used to identify the associations of distinct VAT measures with LA volume (indexed) and deformational indices of global LA strain (i.e. PALS), LA stiffness, global LA reservoir (SRs), conduit (SRe), and booster function (SRa), with clinical co-variates of age, sex, SBP, heart rate, lifestyles including active smoking, alcohol use, regular exercise, and medical history of hypertension, diabetes, and CVD. To eliminate the possible confounding effects of body fat burden, LV filling pressure, or several cardiometabolic profiles on LA structural/functional indices, we

Figure 1 Schematic illustration and delineation of region-specific visceral adiposity fat depots and LA strain/strain rate measures. Delineation on the boundary and region of interest on the definition of quantifying all visceral adiposity fat measures (A). Pericardial fat (PCF), right ventricle (RV), thoracic peri-aortic adipose tissue (TAT), and peri-aortic root fat (PARF) surrounding the aortic root in front of left atrium region (B–D). Case examples from study subjects with low PARF (13.2 mL) and larger PALS (62.4%), LA SRs, and SRe (E), and another participant with high PARF burden (28.4 mL) and lower PALS (25.8%), LA SRs, and SRe (F). Arrows denoted values for peak PALS, and LA strain rate curves (SRs, SRe, and SRa) from three distinct phases (E, F). Ao, aorta; LA, left atrial; LMC, left main coronary artery; LV, left ventricle; PA, pulmonary artery; PALS, peak atrial longitudinal systolic strain; SR, strain rate.

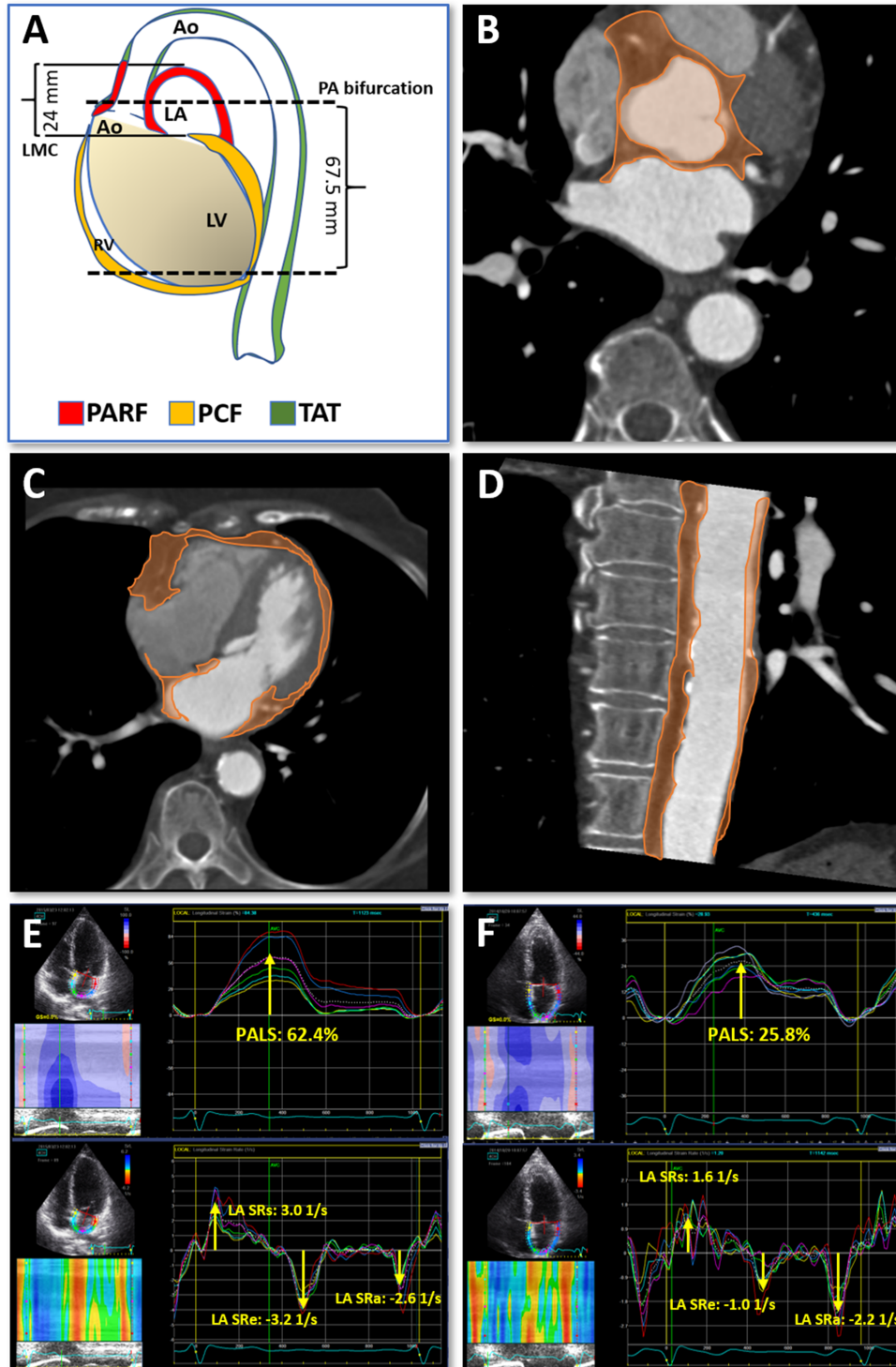


Table 1 Baseline demographic information and conventional ventricular structures/functions stratified by tertiles of peri-aortic root fat

PARF (mL)	All study participants (n = 1326)			PARF Tertile 1 <15.3 (n = 447)	PARF Tertile 2 15.3–24.3 (n = 437)	PARF Tertile 3 >24.3 (n = 442)	P-value (trend)
Baseline characteristic							
Age (years)	51.63 ± 9.32	49.02 ± 8.84	51.75 ± 8.82	54.08 ± 9.59			<0.001
Sex (female) (%)	24.85	42.3	18.3	13.6			<0.001
Systolic BP (mmHg)	123.36 ± 16.73	118.3 ± 16.5	123.4 ± 16.1	128.3 ± 16.1			<0.001
Diastolic BP (mmHg)	76.04 ± 10.92	72.4 ± 10.9	76.0 ± 10.1	79.7 ± 10.6			<0.001
Resting heart rate (beats/min)	73.17 ± 10.03	72.6 ± 10.1	72.9 ± 9.7	74.0 ± 10.3			0.052
Waist circumference (cm)	84.75 ± 9.63	77.65 ± 7.30	85.17 ± 7.26	91.39 ± 8.79			<0.001
Weight (kg)	68.74 ± 12.19	60.84 ± 9.82	69.27 ± 9.48	76.00 ± 12.00			<0.001
Body mass index (kg/m ²)	24.72 ± 3.47	22.37 ± 2.59	24.72 ± 2.56	27.03 ± 3.45			<0.001
TBF (kg)	17.83 ± 6.46	23.3 ± 6.1	25.5 ± 6.3	28.2 ± 6.7			<0.001
Laboratory data							
Sugar (fasting) (mg/dL)	103.08 ± 23.24	96.6 ± 13.2	103.3 ± 19.7	109.6 ± 31.4			<0.001
Insulin (μIU/mL)	8.79 ± 4.99	6.87 ± 3.60	8.69 ± 4.47	10.51 ± 5.74			<0.001
TG (mg/dL)	136.7 ± 86.49	106.11 ± 62.32	147.44 ± 90.11	156.53 ± 94.98			<0.001
Total cholesterol (mg/dL)	204.02 ± 36.24	200.43 ± 34.55	205.11 ± 35.11	206.5 ± 38.7			0.048
HDL (mg/dL)	53.07 ± 14.34	59.17 ± 14.49	51.25 ± 14.15	48.81 ± 12.21			<0.001
LDL (mg/dL)	132.79 ± 33.54	127.52 ± 32.20	134.31 ± 32.77	136.52 ± 34.97			<0.001
Uric acid (mg/dL)	6.02 ± 1.44	5.44 ± 1.36	6.21 ± 1.41	6.42 ± 1.35			<0.001
eGFR (mL/min/1.73 m ²)	86.48 ± 15.21	89.29 ± 15.39	85.55 ± 14.5	84.61 ± 15.34			<0.001
White blood cells (×10 ³ /μL)	6.09 ± 1.57	5.68 ± 1.58	6.19 ± 1.6	6.40 ± 1.45			<0.001
hs-CRP ^a	0.09 (0.045–0.21)	0.04 (0.022–0.092)	0.06 (0.026–0.139)	0.136 (0.061–0.32)			<0.001
VAT							
PCF (mL)	76 ± 29.74	51.8 ± 16.3	73.6 ± 17.4	102.9 ± 27.7			<0.001
TAT (mL)	7.2 ± 3.86	4.3 ± 1.9	7.0 ± 2.6	10.3 ± 4.0			<0.001
Electrocardiography							
PR interval (ms)	165.38 ± 22.6	163.1 ± 20.3	165.2 ± 23.0	167.9 ± 24.1			<0.001
QRS duration (ms)	90.18 ± 10.96	87.9 ± 10.5	91.2 ± 11.3	91.5 ± 10.7			<0.001
QT interval (corrected) (ms)	417.84 ± 22.5	417.3 ± 23.6	416.0 ± 21.8	420.2 ± 22.0			0.018
Medical history							
Hypertension (%)	20.03	8.7	19.2	32.4			<0.001
Diabetes (%)	6.1	2.9	6	9.5			<0.001
Gout (%)	3.16	1.3	3.7	4.5			0.02
Cerebrovascular disease (%)	7.45	0.5	0.5	0.9			0.61
Coronary artery disease (%)	3.39	2	2.3	5.9			0.002
Conventional echocardiography							
IVSd (mm)	9.14 ± 1.07	8.67 ± 1.03	9.16 ± 1.02	9.58 ± 0.96			<0.001
LVEDV (mL)	77.13 ± 12.68	72.64 ± 13.51	77.48 ± 11.48	81.2 ± 11.48			<0.001
LVM indexed to BSA (g/m ^{2.7})	76.45 ± 13.63	72.70 ± 13.35	76.61 ± 13.28	79.99 ± 13.3			<0.001
LVM indexed to Ht ^{2.7} (g/m ^{2.7})	37.0 ± 7.8	33.8 ± 7.0	37.1 ± 7.3	40.2 ± 7.8			<0.001
LVEF (%)	62.57 ± 4.87	63.29 ± 4.68	62.46 ± 4.84	61.96 ± 5.01			0.0011
E/A ratio	1.21 ± 0.40	1.35 ± 0.43	1.19 ± 0.36	1.08 ± 0.34			<0.001

(Continues)

Table 1 (continued)

PARF (mL)	All study participants (n = 1326)	PARF Tertile 1 <15.3 (n = 447)	PARF Tertile 2 15.3–24.3 (n = 437)	PARF Tertile 3 >24.3 (n = 442)	P-value (trend)
PARF range, mL (numbers)					
DT (ms)	204.32 ± 38.52	196.3 ± 37.5	204.3 ± 37.5	212.4 ± 39.0	<0.001
IVRT (ms)	91.53 ± 14.55	89.0 ± 13.3	91.9 ± 14.4	93.8 ± 15.5	<0.001
TDI-e' (cm/s)	9.00 ± 2.18	10.03 ± 2.22	8.96 ± 1.97	8.03 ± 1.89	<0.001
TDI-s' (cm/s)	8.23 ± 1.84	8.3 ± 1.4	8.4 ± 2.5	7.9 ± 1.4	0.001
E/TDI-e' (average)	7.22 ± 2.47	6.67 ± 1.96	7.06 ± 2.31	7.92 ± 2.88	<0.001
Maximum LA volume (mL)	30.61 ± 10.88	25.6 ± 7.9	30.8 ± 10.1	35.5 ± 11.9	<0.001
LA volume index (BSA) (mL/m ²)	16.5 ± 5.49	14.90 ± 4.26	16.45 ± 5.46	18.13 ± 6.10	<0.001
LA volume index (Ht ^{2.7}) (mL/m ^{2.7})	7.8 ± 2.9	6.7 ± 2.2	7.8 ± 2.9	8.9 ± 3.3	<0.001
LAEF (%)	57.38 ± 11.19	56.7 ± 12.0	56.1 ± 10.9	55.2 ± 11.5	0.046
LA deformational assessment					
LA stiffness index	0.21 ± 0.10	0.17 ± 0.07	0.21 ± 0.10	0.25 ± 0.12	<0.001
PALS (%)	36.58 ± 8.09	40.03 ± 7.55	36.34 ± 7.79	33.42 ± 7.54	<0.001
Reservoir SRs (1/s)	1.64 ± 0.38	1.76 ± 0.39	1.63 ± 0.35	1.52 ± 0.37	<0.001
Conduit SRs (1/s)	-1.64 ± 0.54	-1.95 ± 0.54	-1.61 ± 0.46	-1.37 ± 0.44	<0.001
Contractile SRa (1/s)	-2.01 ± 0.49	-2.01 ± 0.48	-2.04 ± 0.48	-1.98 ± 0.50	0.048

A, late mitral inflow diastolic velocity; BP, blood pressure; DT, deceleration time; TDI-e', early mitral annular relaxation velocity; E, early mitral inflow diastolic velocity; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; IVRT, isovolumic relaxation time; IVSd, end-diastolic interventricular septum thickness; LAEF, left atrial emptying fraction; LDL, low-density lipoprotein; LV, left ventricular/left ventricle; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVDD, left ventricular end-diastolic diameter; LVM, left ventricular mass; LVMI, left ventricular mass index; PARF, peri-aortic root fat; PCF, pericardial fat; TDI-s', mitral annular systolic velocity; TAT, thoracic peri-aortic adipose tissue; TBF, total body fat; TG, triglyceride; UA, uric acid; VAT, visceral adiposity.

*Median and interquartile range (25th to 75th) presented.

further adjusted TBF, LV E/TDI-e', and the presence of MetS with age, gender, body mass index (BMI), heart rate, estimated glomerular filtration rate, active smoking, alcohol use, exercise, and CVD as another model (Table 2). We further explored the prognostic implication of VAT on the clinical endpoint of incident AF/HF using Cox regression analysis (Table 3), where MetS and LV E/TDI-e' again were subsequently entered into models (Table 3). We further tested the impact of VAT and PALS data on the probability (compared by log-rank test) of clinical endpoint (AF/HF incidence) by stratifying various VAT and PALS tertiles. By selecting outcome-driven VAT cut-offs using receiver operating characteristic curve, we tested whether adding excessive VAT to abnormal PALS (<23%) may significantly expand the prediction models by likelihood ratio test, with individual odds ratio (OR) and chi-square (χ^2) values reported.

Mediator analysis was performed to examine potential effects of several key cardiometabolic factors (such as TG, HDL, and sugar) in the association of VAT with LA dysfunction. The relationship between VAT, senescence, MetS, and myocardial functions has been investigated,^{2,18,19} with most studies adopting linear correlation for statistical analysis. As mediation analysis may yield a causal model based on a predefined causal relation to determine the direction and size of the effect in cross-sectional studies, we also applied bootstrapping analysis²⁰ to ensure the role of TG, HDL, and sugar as potential mediators. The definitions of mediation and methods in biomedical statistical studies are detailed in the Supporting Information.

All statistical analyses were performed using Statistical Analysis System Version 9.4 (SAS Institute Inc., Cary, NC, USA) and STATA Version 14.0 (Stata Corp LP, College Station, TX, USA), with significance set at $P < 0.05$.

Results

Baseline characteristics and echocardiography by peri-aortic root fat tertiles

Demographic characteristics and conventional echocardiography data according to PARF tertiles from 1326 study participants are presented in Table 1. More advanced age, male sex, higher BP, greater waist circumference, higher TBF, greater BMI, and more unfavourable electrocardiography presentations (ECG) were observed with greater PARF tertiles (all $P < 0.001$). Higher insulin levels, higher TG, low-density lipoprotein, uric acid, lower HDL, and estimated glomerular filtration rate were also observed across greater PARF strata (all $P < 0.001$) (Table 1). Marked increase of PCF and TAT was observed across larger PARF tertiles (both P for trend: <0.001), with greater PARF positively correlated with PCF and TAT ($R = 0.81$ and 0.70 , both $P < 0.001$). Subjects with higher

PARF were more likely to have hypertension, diabetes, gout, and coronary artery disease (all $P < 0.05$) (Table 1). Older age was positively associated with larger PCF, TAT, and PARF ($r = 0.29, 0.38, \text{ and } 0.29$, all $P < 0.001$). In general, increasing PARF by tertiles was associated with unfavourable LV remodelling, greater LV mass, lower TDI-s', larger LA volumes (with/without index), lower TDI-e', more prolonged DT/IVRT, more impaired LA mechanical properties (lower PALS, higher LA stiffness, and worsened SR components), and higher E/TDI-e' (Table 1, all $P < 0.05$). Compared with those without VAT, subjects included in the current study showed subtle and significantly lower PALS ($37.9 \pm 8.1\%$ vs. $36.6 \pm 8.1\%$, $P < 0.001$), although prevalent abnormal PALS (<23%) did not differ significantly between groups (Supporting Information, Figure S2).

Associations of visceral adiposity with metabolic profiles

To examine whether VAT may be independently associated with individual component of MetS (such as BP, fasting sugar, TG, HDL levels, or waist) beyond BMI and TBF, we performed linear regressions on these associations. VAT of non-cardiac region TAT was strongly associated with lower HDL, higher TG, higher fasting glucose, and larger waist after adjusting for age, sex, BMI, and TBF, with larger PARF independently related to higher TG, sugar, and waist (Figure 2, all $P < 0.05$); instead, larger PCF was only associated with higher BP independent of BMI and TBF measure. Per 1 standardized increase of PARF, PCF and TAT were independently associated with higher risk for MetS [adjusted OR: 1.31, 95% confidence interval (CI): 1.08–1.60; 1.25, 95% CI: 1.04–1.50; and 1.52, 95% CI: 1.24–1.86, $P = 0.006, 0.017, \text{ and } <0.001$, respectively]. Higher systemic inflammatory marker hs-CRP along with higher circulating white counts was observed across greater PARF tertiles (Table 1, trend $P: <0.001$), with same trends observed across PCF and TAT tertile groups (0.05, 0.07, and 0.14 for hs-CRP median values, both trend $P: <0.001$).

Associations of visceral adiposity with left atrial kinetics

Data regarding detailed LA structural (LA volume, with/without index) and functional mechanics [PALS, LAEF, global LA stiffness, LA reservoir (SRs), and conduit (SRe)] in relation to PCF and TAT tertiles were further displayed in Supporting Information, Table S2. Overall, greater PARF, PCF, and TAT were associated with worsened PALS, supporting a pathological link between excessive VAT and subclinical LA dysfunction (Supporting Information, Figure S3). In fully adjusted models including all clinical co-variates,

Table 2 Multivariate analysis showing the relationship between adiposity and echocardiography parameters

	LAVI (BSA) (mL/m ²)		LA stiffness		PALS (%)		Reservoir (SRs) (1/s)		Conduit (SRE) (1/s)		Booster (SRa) (1/s)	
	Coef.	P value	Coef.	P value	Coef.	P value	Coef.	P value	Coef.	P value	Coef.	P value
Univariate PARF	0.255	<0.001	0.365	<0.001	-0.371	<0.001	-0.297	<0.001	0.470	<0.001	0.071	0.01
Multivariate Model 1	0.309	<0.001	0.468	<0.001	-0.399	<0.001	-0.326	<0.001	0.627	<0.001	0.187	<0.001
Model 2 + TBF + E/TDI-e'	0.384	<0.001	0.841	<0.001	-0.456	<0.001	-0.466	<0.001	0.701	0.002	0.367	0.018
Model 3 + TBF + MetS + E/TDI-e'	0.374	<0.001	0.837	<0.001	-0.450	<0.001	-0.457	0.001	0.697	0.005	0.350	0.029
Univariate PCF	0.191	<0.001	0.342	<0.001	-0.359	<0.001	-0.279	<0.001	0.449	<0.001	0.075	0.007
Multivariate Model 1	0.245	<0.001	0.438	<0.001	-0.386	<0.001	-0.299	<0.001	0.604	<0.001	0.188	<0.001
Model 2 + TBF + E/TDI-e'	0.363	0.008	0.840	<0.001	-0.458	<0.001	-0.465	<0.001	0.700	0.002	0.368	0.010
Model 3 + TBF + MetS + E/TDI-e'	0.351	0.019	0.837	<0.001	-0.453	<0.001	-0.457	0.001	0.696	0.010	0.353	0.008
Univariate TAT	0.155	<0.001	0.282	<0.001	-0.317	<0.001	-0.219	<0.001	0.449	<0.001	0.001	0.97
Multivariate Model 1	0.244	<0.001	0.422	<0.001	-0.350	<0.001	-0.271	<0.001	0.607	<0.001	0.161	0.002
Model 2 + TBF + E/TDI-e'	0.358	0.160	0.838	0.380	-0.445	0.034	-0.459	0.007	0.700	0.002	0.362	0.420
Model 3 + TBF + MetS + E/TDI-e'	0.347	0.160	0.834	0.743	-0.440	0.125	-0.449	0.025	0.696	0.005	0.346	0.653

All adiposity measures were naturally log-transformed and then standardized to a mean of 0 and an SD of 1 to facilitate comparison of regression coefficients between different fat depots. Model 1: age + gender; Model 2: age, gender, body mass index, systolic blood pressure, heart rate, estimated glomerular filtration rate, active smoking, alcohol use, exercise, hypertension, diabetes, and cardiovascular disease; Model 3: age, gender, body mass index, heart rate, estimated glomerular filtration rate, active smoking, alcohol use, exercise, and cardiovascular disease. Variance inflation factor was <2 in all models. Coef., coefficient; LA, left atrial/left atrium; MetS, metabolic syndrome; PALS, peak atrial longitudinal systolic strain; PARF, peri-aortic root fat; PCF, pericardial fat; TAT, thoracic peri-aortic adipose tissue; TBF, total body fat; SR, strain rate.

Table 3 Cox models showing associations of various visceral adiposity measures with composite outcomes (including atrial fibrillation/heart failure)

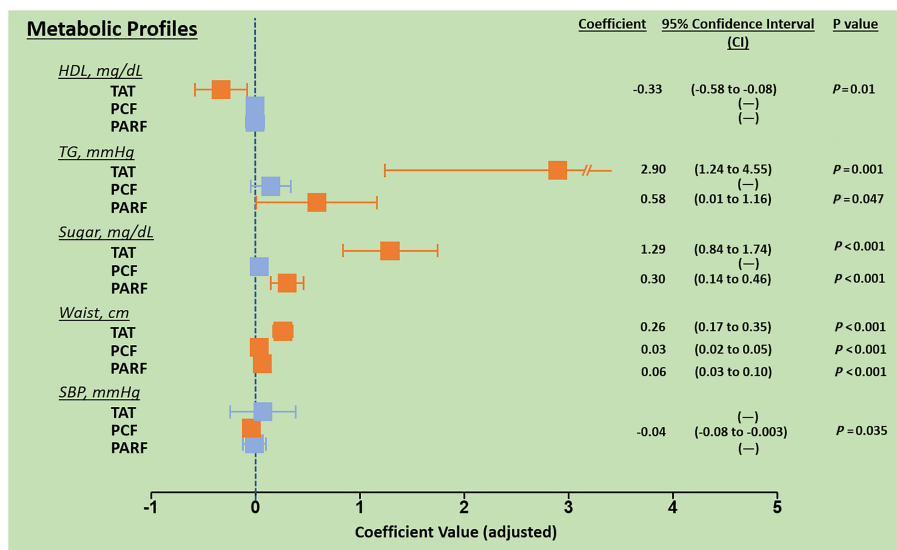
Endpoint by Cox regression models		HF/AF	
Event number/rate	63 (4.7%)		
PARF (per +1 Z score)	HR	(95% CI)	P value
Crude	2.23	(1.86–2.68)	<0.001
Multivariate Model 1 + E/TDI-e'	1.7	(1.29–2.24)	<0.001
Multivariate Model 2 + MetS + E/TDI-e'	1.56	(1.17–2.08)	0.002
PCF (per +1 Z score)	HR	(95% CI)	P value
Crude	2.08	(1.73–2.50)	<0.001
Multivariate Model 1 + E/TDI-e'	1.33	(1.02–1.73)	0.034
Multivariate Model 2 + MetS + E/TDI-e'	1.20	(0.92–1.577)	0.18
TAT (per +1 Z score)	HR	(95% CI)	P value
Crude	1.72	(1.44–2.04)	<0.001
Multivariate Model 1 + E/TDI-e'	1.03	—	—
Multivariate Model 2 + MetS + E/TDI-e'	1.00	—	—

Model 1: age, sex, body mass index, estimated glomerular filtration rate, and history of hypertension, diabetes, and cardiovascular disease; Model 2: age, sex, body mass index, estimated glomerular filtration rate, and cardiovascular disease. AF, atrial fibrillation; CI, confidence interval; HF, heart failure; HR, hazard ratio; MetS, metabolic syndrome; PARF, peri-aortic root fat; PCF, pericardial fat.

TBF composition and E/e', independent associations were observed among greater VAT, larger LAVi, and worse PALS and phasic global LA reservoir (SRs)/conduit (SRe) kinetics (Table 2). However, in an alternative model incorporating MetS, TBF composition, and LV E/TDI-e', these associations became attenuated or insignificant in TAT, with both higher cardiac region VAT of PARF and PCF associated with functional decline of PALS (Coef: -0.45 for PARF/PCF, both $P < 0.001$), higher LA stiffness (0.84 for PARF/PCF, both $P < 0.001$), and deteriorated LA SR components (all $P < 0.05$). No significant interaction was found between sex and adiposity measures in the LA deformation index (all $P_{\text{interaction}} = \text{NS}$).

Mediators of obesity and cardiovascular function

After adjustment for age and sex, we confirmed that the potential mediators TG, HDL, and sugar level were related to PCF, TAT, and PARF (Supporting Information, Table S3). In our mediator analysis, TG, HDL, and fasting glucose explained 9.9%, 6.3%, and 5.0%; 7.4%, 9.8%, and 1.9%; and 11.7%, 10.2%, and 2.8% of the mediating effects in the relationships of PARF with PALS, SRs (reservoir), and SRe (conduit), respectively (Supporting Information, Figure S4). Overall, TG, HDL, and fasting sugar showed larger mediating effects in the relationships between TAT with PALS, SRs (reservoir), and SRe (conduit). Co-mediation analysis showed that combined three

Figure 2 Associations of region-specific visceral adiposity with metabolic components. Linear associations of various visceral adiposity [peri-aortic root fat (PARF), pericardial fat (PCF), and TAT] with each metabolic component after adjusting for age, sex, body mass index, and body fat, with coefficient values, 95% confidence intervals (CIs), and P values presented. HDL, high-density lipoprotein; SBP, systolic blood pressure; TG, triglyceride.

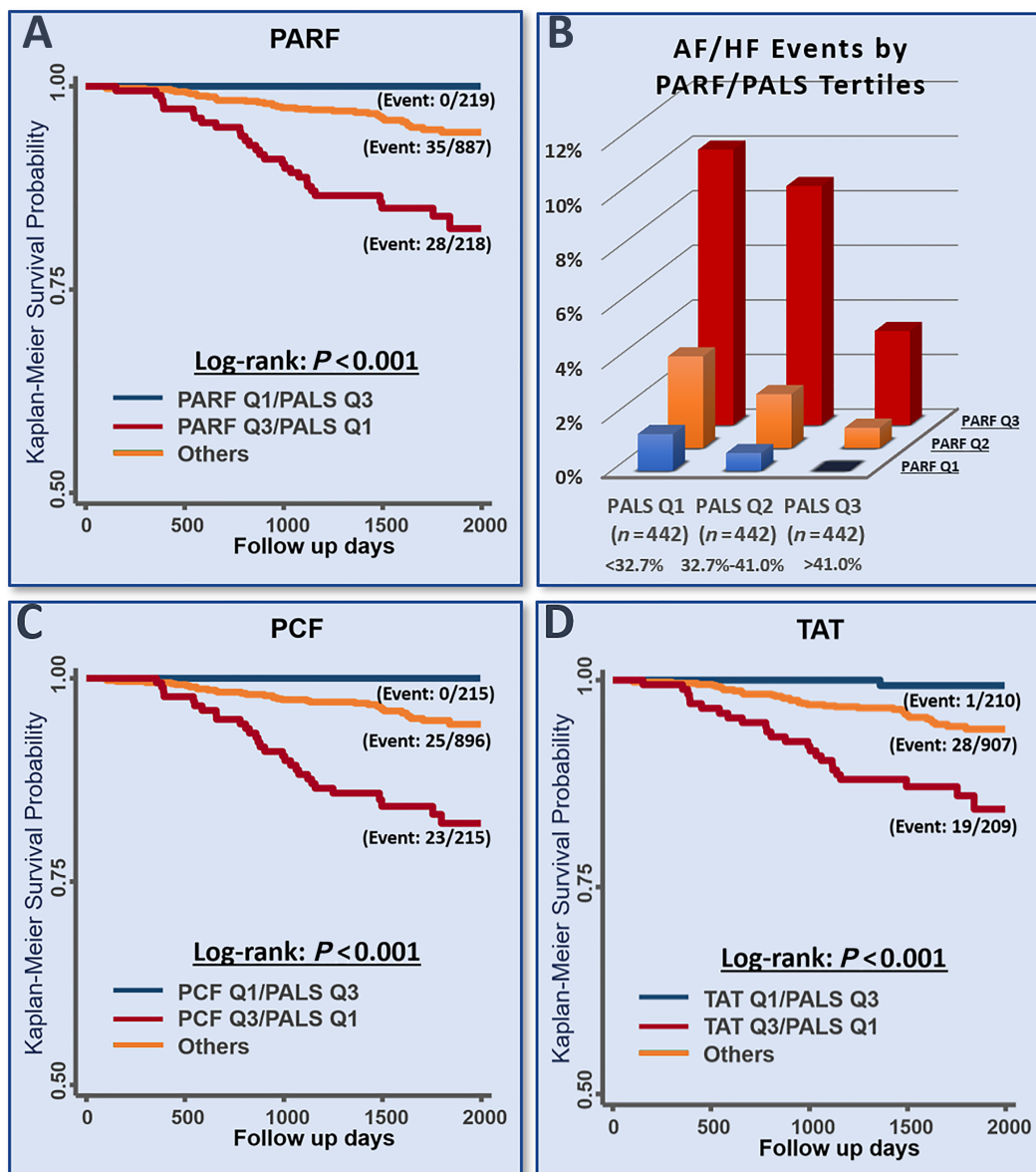
circulating metabolic profiles (TG + HDL + glucose) explained 13.7%, 13.3%, and 16.3% of the mediating effects in the relationships of PARF with PALS, SRs, and SRe, respectively (Supporting Information, *Figure S4*). These mediating effects were broadly significant. Overall, TG, HDL, and fasting sugar showed larger mediating effects in the relationships between TAT with PALS, SRs (reservoir), and SRe (conduit). The bootstrapping method validated that all the mediators were statistically significant in the relationships between various adiposity measures with LA PALS, reservoir, and conduit functions (the 95% CI did not include 0) (Supporting Information,

Table S4). By categorizing study participants by BMI, those classified into more severe degree of obesity consistently showed graded and significantly larger VAT (PCF, TAT, and PARF), more impaired LA mechanical properties, and developed higher AF and HF events (Supporting Information, *Table S5*).

Clinical endpoints

Over a median of 1790 days (interquartile range: 25th to 75th: 1440–1927 days) of follow-up, 63 subjects developed

Figure 3 Event-free probability based on region-specific visceral adiposity and PALS tertiles. Kaplan–Meier survival curves demonstrating event-free probability for incident atrial fibrillation (AF)/heart failure (HF) using peri-aortic root fat (PARF) adiposity and peak atrial longitudinal systolic strain (PALS) strata (A), and bars of event rates by integrated PARF/PALS tertiles (B), as well as Kaplan–Meier survival curves by pericardial fat (PCF)/TAT and PALS strata (C, D). Q1–Q3 represent first to third tertile groups, respectively.



either AF ($n = 33$) or HF ($n = 48$). Each increment of PARF, PCF, and TAT was associated with a greater risk of AF/HF incidence (Table 3) by a Cox regression model, with PARF and PCF remaining consistently significant after accounting for baseline characteristics of age, sex, BMI, BP, known medical histories of hypertension, diabetes, and CVD, but not TAT ($P = 0.26$), with similar trends after adjusting for LV mass and LAEF. By categorizing PALS into tertiles, subjects at the highest PARF adiposity and lowest PALS tertile groups experienced significantly higher clinical endpoints compared with the highest PALS and lowest PARF measures (Figure 3A and 3B, $P_{\text{interaction}} = \text{NS}$ for modifying effects of PARF on PALS). Similar trends were observed by stratifying study participants into PCF/PALS or TAT/PALS tertiles (Figure 3C and 3D). Finally, adding optimal PCF/PARF cut-offs (>86.4 and >23.6 mL, respectively) to abnormal PALS ($<23\%$) successfully expanded the model prediction [χ^2 : 10.8, OR: 4.31, 95% CI: 2.01–9.25 for abnormal PALS to 46.1, OR: 6.15, 95% CI: 3.48–10.86, and 46.7, OR: 6.29, 95% CI: 3.44–11.53, after adding PCF and PARF cut-offs to abnormal PALS, both $P < 0.001$] for AF/HF events at long-term (at 5 years) follow-up (Figure 4).

Discussion

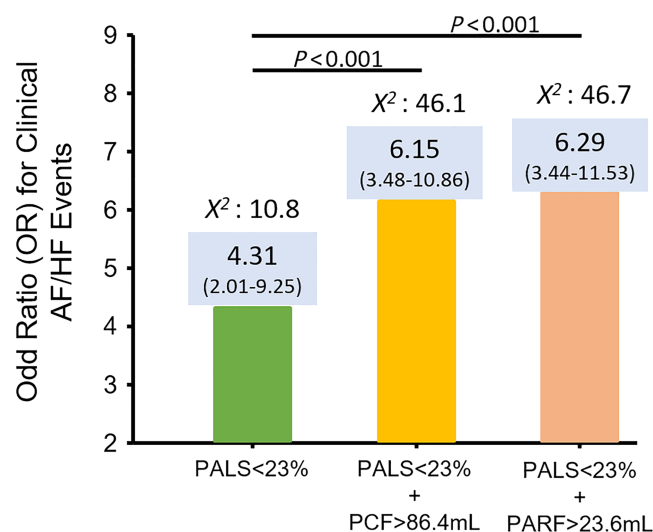
In the current study, we showed that excessive visceral fat may cause significant detrimental effects on LA structures and functions in fully adjusted model including body fat, BMI, and E/TDI-e', with fat surrounding cardiac region (i.e. PARF/PCF) exerted independent effects when MetS were

incorporated into models; instead, peri-aortic adiposity (TAT) showed stronger independent and positive links to circulating cardiometabolic factors including HDL, TG, and sugar levels when body fat and BMI were adjusted. Mediator analysis showed in general larger mediating effects of HDL and TG between all VAT and altered diverse LA functional indices that appeared to be more pronounced in TAT, with relatively minor contribution by fasting glucose. During follow-up, visceral fat of PARF surrounding LA region remained independent predictor in the development of AF or HF when MetS and LV E/TDI-e' were taken into account.

Region-specific visceral adiposity and cardiovascular risks

Obesity, defined by excessive body fat or adiposity using BMI measure, is a well-known risk factor for HF and AF incidence and plays a central key role in HFpEF pathophysiology.²¹ Except for its haemodynamic effects, BMI *per se*, however, comprises both fat and non-fat fractions (e.g. lean muscle mass) and therefore fails to reflect true total adiposity burden and precise partitioning and may not be an optimal clinical surrogate to define excessive adiposity.³ The classic concept of visceral adipose tissue surrounding vital organs (e.g. those in direct contact with the heart) under physiological conditions may include its role as lipogenic capacity for local energy store and mechanical protection of the heart²² and likely serve as source of energy reserve in highly catabolic chronic disorders known as 'obesity paradox'.²³ On the other

Figure 4 Prognostic utilization by adding visceral adiposity of TAT and peri-aortic root fat (PARF) to peak atrial longitudinal systolic strain (PALS). Adding visceral adiposity cut-offs of pericardial fat (PCF) (>86.4 mL) and PARF (>23.6 mL) to abnormal left atrial strain ($<23\%$) expanded the risk models for predicting combined atrial fibrillation (AF)/heart failure (HF) events.

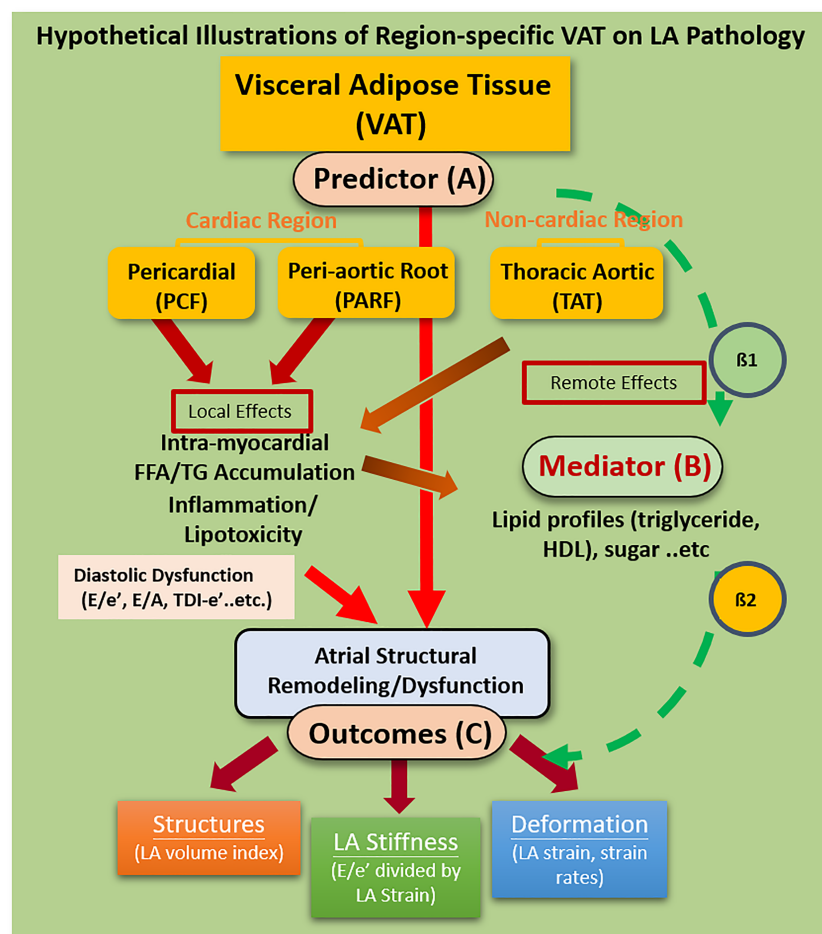


hand, VAT as biologically active endocrine organ capable of buffering excessive energy intake has been proposed to be a key player in determining metabolic disturbances, pro-inflammatory adipokines secretion, and cardiovascular events.⁸ Aging and obesity from calorie-rich diet tightly linked to MetS had shown to involve differential lipid and microbiome changes that may widely impact on immune condition and elicited systemic inflammatory responses as possible mechanism for HF development.²⁴ In this regard, continuous expansion of dysregulated VAT from positive energy balance may cause free fatty acid (FFA) overload resulting in toxic fatty acid saturation (e.g. paracrine actions) that enable local paracrine effects on vital organs (e.g. heart or liver²⁵). More recent advances in imaging modalities and techniques have rendered more precise VAT distribution (region-specific) and quantification assessable beyond subcutaneous or lean body mass, which has substantially improved the understanding of region-specific effects (remote or local) of VAT depots in distinct CVD.^{26,27}

Hypothetical mediating effects of circulating metabolic profiles between region-specific visceral fat and left atrial dysfunction

Free fatty acid as the primary myocardial energy source from circulating TG influx/uptake to generate myocardial energy is temporarily stored in hypertrophied adipocytes within visceral fat as triacylglycerols (or TG) lipid droplets when a positive energy balance is met.^{8,9} It has been therefore proposed that lipid intermediates, such as HDL or TG, may signal biological triacylglycerol turn-over and serve as mediators of VAT in MetS,^{7,28} with excessive myocardial TG storage from upstream free fatty acid overload or under-utilization shown to exert cardiac lipotoxicity causing subclinical LV dysfunction in type 2 diabetes.^{8,29} In this regard, higher TG level can be viewed as a remote circulating marker of failure in buffering excessive TG from saturated VAT capacity. Conversely, recent molecular evidence has also indicated that HDL can resist oxidative stress and protect cardiomyocytes³⁰ by serving as a

Figure 5 Pathophysiological framework and mediation effect between visceral adiposity and left atrium function. Conceptual framework illustrating hypothetical influences of visceral adiposity (VAT) fat on diastolic and atrial structure/function using different metrics and the mediating effects in modelling. FFA, free fatty acid; HDL, high-density lipoprotein; LA, left atrial; PARF, peri-aortic root fat; PCF, pericardial fat; TG, triglyceride.



scavenger to reverse imbalanced lipid/energy metabolism and likely provides key beneficial regulatory effects via neuro-hormonal inactivation.³¹ In aggregate, we speculated that both TG and HDL may therefore serve as markers or play essential roles in regulating myocardial homeostasis and functions through their remote effects. Interestingly, we observed independent associations of higher TAT with lower HDL, higher TG or fasting glucose but not PCF, with larger PARF independently related to higher TG, sugar, and waist. Overall, TG/HDL and glucose appeared to show larger intermediary effects between TAT and LA mechanical indices compared with PARF/PCF, implying that TAT as visceral fat near the central aortic area may rely on these metabolic profiles to a greater degree in regulating myocardium than PARF/PCF (*Figure 5*).

Associations of region-specific visceral adiposity and left atrial structural/functional alterations

Excessive accumulation of adiposity surrounding the heart may directly impede LV filling through a local physical constraint and impair diastolic mechanical properties.³² Furthermore, a great body of literatures have also demonstrated direct and local negative impacts on myocardial tissue from VAT through elicited oxidative stress and several pathological pro-inflammatory mechanisms with excessive LA interstitial fibrotic replacement, causing 'atrial myopathy' prone to AF onset or perpetuation,^{6,13,19,33} leading to HFpEF/AF development.^{33,34} Indeed, independent pathological links were observed between abundant epicardial adiposity and structural atrial dilation³⁵ or subclinical impaired LA mechanics by either speckle-tracking or MRI assessment.^{14,36,37} However, these studies were limited by relatively small number and lack of comprehensive LA measures or follow-up data. Under normal physiological status, left atrium plays a central role in modulating cardiac performance by interacting with passive LV filling with three distinct phasic components throughout one cardiac cycle including reservoir, conduit, and active booster pump.³⁸ Despite complex LA kinetics observed, deformational imaging analysis can be readily used to assess these physiological and pathologic states.¹⁶ In the present study, we observed that VAT of cardiac region (i.e. PARF/PCF) remained independently associated with adverse LA kinetics even when body fat, MetS, and LV E/TDI-e' were adjusted (*Table 2*), indicating detrimental effects of PARF/PCF on LA kinetics beyond body fat partitions and LV filling status (*Figure 4*). Instead, the independent associations between TAT and LA kinetics were largely attenuated when the presence of metabolic derangements (containing TG, HDL, and sugar information) was entered into model. These findings, when taken collectively with the observed stronger mediating effects of metabolic profiles between TAT and LA mechanics, may imply that VAT without anatomic contact

with myocardium (i.e. TAT) may confer its negative effects mainly from cardiometabolic mediators remotely. On contrary, while cardiac region VAT of PCF or PARF were either confined to the pericardial sac adjacent or in close spatial relation to the atrium (especially PARF), VAT of these regions could exert more direct local pathological biological effects.¹⁴

Study limitations

Our study has several limitations. First, male sex was predominant in this study, partly because men were more willing to undergo MDCT owing to their higher coronary risk. Secondly, although we did observe that visceral fat (PCF, TAT, and PARF) affected LA functions through the mediating effects of TG, HDL, and sugar level, the role of blood sugar as a mediator between visceral fat and LA function was relatively weak (2–6%). The study participants mainly comprised a lower risk population undergoing the health survey, and thus, blood sugar may not play a dominant role in mediating unfavourable cardiac effects at such an early, pre-clinical stage. Hence, further research should examine individuals across a broader spectrum of CVD to confirm these associations.

Conclusions

Our current study revealed that region-specific visceral fat depots likely exert diverse biological effects on cardiometabolic health and widely influence LA structure and function at a pre-clinical stage. Ectopic visceral fat surrounding the heart, especially those near atrial region, may have a direct and greater impact on LA remodelling and several functional atrial surrogates for HF or AF pathophysiology. However, VAT near the aortic area are tightly associated with cardiometabolic profiles and more likely mediate their toxic effects mainly through remote and circulating metabolic profiles.

Perspectives

Clinical competencies

As the global burden of HFpEF and AF continues to increase dramatically due to rapid global aging and obesity, our findings offer an opportunity for early recognition of potential targets that tightly link to atrial cardiomyopathy and likely improve individualized risk stratification. Furthermore, insights on the observed disparities underlying region-specific VAT and atrial functions may represent certain clinical HFpEF phenotypes mainly affecting atrial functions and likely serve as useful clinical surrogates for subsequent successful

pharmacological/surgical interventions or lifestyle modifications. For example, recent clinical trials have demonstrated the beneficial effects of sodium glucose co-transporters 2 inhibitors in reducing burden of body mass, metabolic disturbances, and favourable HF outcomes in diabetes,³⁹ with hypothetical key therapeutic interventions targeting on VAT reduction. Early identification of a specific population at higher risk for subsequent HF development with phenotypic obesity or those featured by metabolic derangements moving towards precision medicine may therefore facilitate more aggressive pharmacological treatment.

Translational outlook

The current study hypothesis was based on relevant research and was established within a framework of causal relationships from mediation analysis, which may contribute substantially to the knowledge and exploration of pathway-specific signalling in the pathogenesis of atrial cardiomyopathy by excessive VAT accumulation or in certain obese-related HFpEF at higher risk of incident AF/HFpEF. The differential effects of region-specific adiposity on various cardiovascular disorders beyond phenotypic obesity may also require further experimental research at a molecular basis to verify and elucidate the precise pathological mediation involved. Finally, our current study may also implicate the initiation of innovative precision medicine and personalized approached to deliver primary preventive therapeutic strategies.

Acknowledgement

We especially thank Bernard Bulwer's contribution of the schematic illustrations of the different cardiac geometries presented in this study.

Conflict of interest

None declared.

References

1. Palmer AK, Kirkland JL. Aging and adipose tissue: potential interventions for diabetes and regenerative medicine. *Exp Gerontol* 2016; **86**: 97–105.
2. Hunter GR, Gower BA, Kane BL. Age related shift in visceral fat. *Int J Body Compos Res* 2010; **8**: 103–108.
3. Jensen MD. Role of body fat distribution and the metabolic complications of obesity. *J Clin Endocrinol Metab* 2008; **93**: S57–S63.
4. Goldani H, Adami FS, Antunes MT, Rosa LH, Fassina P, Quevedo Grave MT, Morelo Dal Bosco S. Applicability of the

Funding

This work was partially funded by grants from the National Science Council (NSC 101-2314-B-195-020, 103-2314-B-010-005-MY3, 103-2314-B-195-001-MY3, 101-2314-B-195-020-MY1, MOST 103-2314-B-195-006-MY3), MacKay Memorial Hospital (10271, 10248, 10220, 10253, 10375, 10358, E-102003), and the Taiwan Foundation for Geriatric Emergency and Critical Care.

Supporting information

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

Figure S1. Mediators between visceral obesity and LA dysfunction [1].

Figure S2. LA strain (PALS) was slightly yet statistically significantly lower in subjects with VAT eligible for current study compared to the cohort without VAT (left panel) ($36.6 \pm 8.1\%$ vs. $37.9 \pm 8.1\%$, $p < 0.001$). Prevalent abnormal PALS ($< 23\%$) did not differ significantly between groups (right panel).

Figure S3. The associations of PARF, PCF and TAT with PALS by 3 knots restricted cubic spline analysis (unadjusted) with selected based on tertile cut-point in addition to the lower (5th) and upper (95th) percentile threshold values for each visceral adiposity measure (B-D). Fully adjusted models between visceral adiposity and LA deformational measures were presented in Table 2 in text.

Figure S4. Illustration of mediating effect (β denotes regression coefficient). Potential mediators of association between of various ectopic visceral fat depots and left atrial function.

Table S1. Comparisons of baseline characteristics of study subjects included and not included in current study cohort.

Table S2. Conventional LA echocardiography parameters and deformations stratified by tertiles of PCF and TAT.

Table S3. Age- and sex-adjusted Pearson's correlations between potential mediators, adiposity, and echocardiography parameters.

Table S4. 95% Confidence intervals by bootstrapping analysis

Table S5. Visceral fat and LA mechanical properties and AF/HF incident stratified by WHO Asian Criteria-BMI.

- visceral adiposity index (VAI) in the prediction of the components of the metabolic syndrome in elderly. *Nutr Hosp* 2015; **32**: 1609–1615.
5. Cañon-Montañez W, Santos ABS, Nunes LA, Cañon-Montañez W, Santos ABS, Nunes LA, Pires JCG, Freire CMV, Ribeiro ALP, Mill JG, Bessel M, Duncan BB, Schmidt MI, Foppa M. Central obesity is the key component in the association of metabolic syndrome with left ventricular global longitudinal strain impairment. *Rev Esp Cardiol* 2017; **71**: 524–530.
 6. Pandit SV, Anumonwo J, Jalife J. Atrial fibrillation susceptibility in obesity: an excess adiposity and fibrosis complicity? *Circ Res* 2016; **118**: 1468–1471.
 7. Calabuig A, Barba J, Guembe MJ, Díez J, Berjón J, Martínez-Vila E, Irimia P, Toledo E. Epicardial adipose tissue in the general middle-aged population and its association with metabolic syndrome. *Rev Esp Cardiol* 2017; **70**: 254–260.
 8. González N, Moreno-Villegas Z, González-Bris A, Egido J, Lorenzo Ó. Regulation of visceral and epicardial adipose tissue for preventing cardiovascular injuries associated to obesity and diabetes. *Cardiovasc Diabetol* 2017; **16**: 44.
 9. Lopaschuk GD, Ussher JR, Folmes CD, Jaswal JS, Stanley WC. Myocardial fatty acid metabolism in health and disease. *Physiol Rev* 2010; **90**: 207–258.
 10. Matsuura F, Yamashita S, Nakamura T, Nishida M, Nozaki S, Funahashi T, Matsuzawa Y. Effect of visceral fat accumulation on uric acid metabolism in male obese subjects: visceral fat obesity is linked more closely to overproduction of uric acid than subcutaneous fat obesity. *Metabolism* 1998; **47**: 929–933.
 11. Chirinos JA, Sardana S, Satija V, Gillebert TC, De Buyzere ML, Chahwala J, De Bacquer D, Segers P, Rietzschel ER, Asklepios investigators. Effect of obesity on left atrial strain in persons aged 35–55 years (The Asklepios Study). *Am J Cardiol* 2019; **123**: 854–861.
 12. Lavie CJ, Pandey A, Lau DH, Alpert MA, Sanders P. Obesity and atrial fibrillation prevalence, pathogenesis, and prognosis: effects of weight loss and exercise. *J Am Coll Cardiol* 2017; **70**: 2022–2035.
 13. Goldberger JJ, Arora R, Green D, Greenland P, Lee DC, Lloyd-Jones DM, Markl M, Ng J, Shah SJ. Evaluating the atrial myopathy underlying atrial fibrillation: identifying the arrhythmogenic and thrombogenic substrate. *Circulation* 2015; **132**: 278–291.
 14. Delgado V, Di Biase L, Leung M, Romero J, Tups LF, Casadei B, Marrouche N, Bax JJ. Structure and function of the left atrium and left atrial appendage: AF and stroke implications. *J Am Coll Cardiol* 2017; **70**: 3157–3172.
 15. Freed BH, Daruwalla V, Cheng JY, Aguilar FG, Beussink L, Choi A, Klein DA, Dixon D, Baldrige A, Rasmussen-Torvik LJ, Maganti K, Shah SJ. Prognostic utility and clinical significance of cardiac mechanics in heart failure with preserved ejection fraction: importance of left atrial strain. *Circ Cardiovasc Imaging* 2016; **9**: e003754.
 16. Liao JN, Chao TF, Kuo JY, Sung KT, Tsai JP, Lo CI, Lai YH, Su CH, Hung CL, Yeh HI, Chen SA. Age, sex, and blood pressure-related influences on reference values of left atrial deformation and mechanics from a large-scale Asian population. *Circ Cardiovasc Imaging* 2017; **10**: e006077.
 17. Yun CH, Longenecker CT, Chang HR, Mok GS, Sun JY, Liu CC, Kuo JY, Hung CL, Wu TH, Yeh HI, Yang FS, Lee JJ, Hou CJ, Cury RC, Bezerra HG. The association among peri-aortic root adipose tissue, metabolic derangements and burden of atherosclerosis in asymptomatic population. *J Cardiovasc Comput Tomogr* 2016; **10**: 44–51.
 18. Libhaber CD, Norton GR, Majane OH, Libhaber E, Essop MR, Brooksbank R, Maseko M, Woodiwiss AJ. Contribution of central and general adiposity to abnormal left ventricular diastolic function in a community sample with a high prevalence of obesity. *Am J Cardiol* 2009; **104**: 1527–1533.
 19. Canepa M, Strait JB, Abramov D, Milanesechi Y, AlGhatrif M, Moni M, Ramachandran R, Najjar SS, Brunelli C, Abraham TP, Lakatta EG, Ferrucci L. Contribution of central adiposity to left ventricular diastolic function (from the Baltimore Longitudinal Study of Aging). *Am J Cardiol* 2012; **109**: 1171–1178.
 20. Henderson AR. The bootstrap: a technique for data-driven statistics. Using computer-intensive analyses to explore experimental data. *Clin Chim Acta* 2005; **359**: 1–26.
 21. Reddy YNV, Carter RE, Obokata M, Redfield MM, Borlaug BA. A simple, evidence-based approach to help guide diagnosis of heart failure with preserved ejection fraction. *Circulation* 2018; **138**: 861–870.
 22. Antonopoulos AS, Antoniadis C. The role of epicardial adipose tissue in cardiac biology: classic concepts and emerging roles. *J Physiol* 2017; **595**: 3907–3917.
 23. Neeland IJ, Poirier P, Després JP. Cardiovascular and metabolic heterogeneity of obesity: clinical challenges and implications for management. *Circulation* 2018; **137**: 1391–1406.
 24. Kain V, Van Der Pol W, Mariappan N, Ahmad A, Eipers P, Gibson DL, Gladine C, Vigor C, Durand T, Morrow C, Halade GV. Obesogenic diet in aging mice disrupts gut microbe composition and alters neutrophil:lymphocyte ratio, leading to inflamed milieu in acute heart failure. *FASEB J* 2019; **33**: 6456–6469.
 25. Fitzgibbons TP, Czech MP. Epicardial and perivascular adipose tissues and their influence on cardiovascular disease: basic mechanisms and clinical associations. *J Am Heart Assoc* 2014; **3**: e000582.
 26. Demerath EW, Sun SS, Rogers N, Lee M, Reed D, Choh AC, Couch W, Czerwinski SA, Chumlea WC, Siervogel RM, Towne B. Anatomical patterning of visceral adipose tissue: race, sex, and age variation. *Obesity* 2007; **15**: 2984–2993.
 27. Hung CL, Yun CH, Lai YH, Sung KT, Bezerra HG, Kuo JY, Hou CJ, Chao TF, Bulwer BE, Yeh HI, Shih SC, Lin SJ, Cury RC. An observational study of the association among inter-atrial adiposity by computed tomography measure, insulin resistance, and left atrial electromechanical disturbances in heart failure. *Medicine* 2016; **95**: e3912.
 28. Al-Sulaiti H, Diboun I, Banu S, Al-Emadi M, Amani P, Harvey TM, Dömling AS, Latiff A, Elrayess MA. Triglyceride profiling in adipose tissues from obese insulin sensitive, insulin resistant and type 2 diabetes mellitus individuals. *J Transl Med* 2018; **16**: 175–113.
 29. Mochizuki Y, Tanaka H, Matsumoto K, Sano H, Toki H, Shimoura H, Ooka J, Sawa T, Motoji Y, Ryo K, Hirota Y, Ogawa W, Hirata K. Clinical features of subclinical left ventricular systolic dysfunction in patients with diabetes mellitus. *Cardiovasc Diabetol* 2015; **14**: 37.
 30. Nagao M, Toh R, Irino Y, Nakajima H, Oshita T, Tsuda S, Hara T, Shinohara M, Ishida T, Hirata KI. High-density lipoprotein protects cardiomyocytes from oxidative stress via the PI3K/mTOR signaling pathway. *FEBS Open Bio* 2017; **7**: 1402–1409.
 31. Mehra MR, Uber PA, Francis GS. Heart failure therapy at a crossroad: are there limits to the neurohormonal model? *J Am Coll Cardiol* 2003; **41**: 1606–1610.
 32. Iacobellis G, Leonetti F, Singh N, Sharma M. Relationship of epicardial adipose tissue with atrial dimensions and diastolic function in morbidly obese subjects. *Int J Cardiol* 2007; **115**: 272–273.
 33. 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**: 1559–1566.
 34. Hu YF, Chen YJ, Lin YJ, Chen SA. Inflammation and the pathogenesis of atrial fibrillation. *Nat Rev Cardiol* 2015; **12**: 230–243.
 35. Mancio J, Azevedo D, Fragao-Marques M, Falcao-Pires I, Leite-Moreira A, Lunet N, Fontes-Carvalho R, Bettencourt N. Meta-analysis of relation of epicardial adipose tissue volume to left atrial dilation and to left ventricular hypertrophy and functions. *Am J Cardiol* 2019; **123**: 523–531.
 36. Evin M, Broadhouse KM, Callaghan FM, McGrath RT, Glastras S, Kozor R, Hocking SL, Lamy J, Redheuil A, Kachenoura N, Fulcher GR, Figtree GA, Grieve SM.

- Impact of obesity and epicardial fat on early left atrial dysfunction assessed by cardiac MRI strain analysis. *Cardiovasc Diabetol* 2016; **15**: 164.
37. Lai YH, Yun CH, Su CH, Yang FS, Yeh HI, Hou CJ, Wu TH, Cury RC, Bezerra HG, Hung CL. Excessive interatrial adiposity is associated with left atrial remodeling, augmented contractile performance in asymptomatic population. *Echo Res Pract* 2016; **3**: 5–15.
38. Hoit BD. Assessing atrial mechanical remodeling and its consequences. *Circulation* 2005; **112**: 304–306.
39. Díaz-Rodríguez E, Agra RM, Fernández AL, Adrio B, García-Caballero T, González-Juanatey JR, Eiras S. Effects of dapagliflozin on human epicardial adipose tissue: modulation of insulin resistance, inflammatory chemokine production, and differentiation ability. *Cardiovasc Res* 2018; **114**: 336–346.