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CLINICAL RESEARCH
Heart failure and cardiomyopathies

Pathophysiologic importance of visceral adipose tissue in women with heart failure and preserved ejection fraction

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Aims Central obesity is a major risk factor for heart failure with preserved ejection fraction (HFpEF), particularly in women, but the mechanisms remain unclear. We hypothesized that sex-specific differences in visceral adipose tissue (VAT) content would differentially relate to haemodynamic severity of HFpEF in women and men.

Methods and results Abdominal computed tomography (CT) and invasive haemodynamic exercise testing were performed in 105 subjects with HFpEF (63 women) and 105 age-, sex-, and body mass index-matched controls. Visceral adipose tissue area was quantified by CT. As compared with control women, VAT area was 34% higher in women with HFpEF (186 ± 112 vs. 139 ± 72 cm^2, $P = 0.006$), while VAT area was not significantly different in men with or without HFpEF (294 ± 158 vs. 252 ± 92 cm^2, $P = 0.1$). During exercise, pulmonary capillary wedge pressure (PCWP) increased markedly and to similar extent in both men and women with HFpEF. Women with increased VAT area displayed 33% higher PCWP during exercise compared with women with normal VAT area (28 ± 10 vs. 21 ± 10 mmHg, $P = 0.001$), whereas exercise PCWP was similar in men with or without excess VAT (24 ± 9 vs. 25 ± 6, $P = 0.89$). In women, each 100 cm^2 increase in VAT area was associated with a 4.0 mmHg higher PCWP (95% CI 2.1, 6.0 mmHg; $P < 0.0001$), but there was no such relationship in men (interaction $P = 0.009$).

Conclusions These data suggest that accumulation of excess VAT plays a distinct and important role in the pathophysiology of HFpEF preferentially in women. Further research is needed to better understand the mechanisms and treatment implications for visceral fat in HFpEF.

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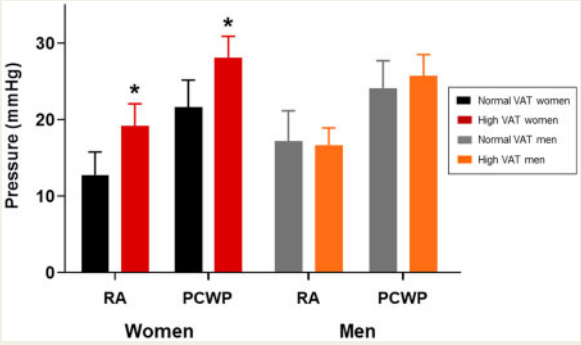
Graphical Abstract



Keywords Visceral adipose tissue • Obesity • Haemodynamics • Heart failure

Introduction

Patients with heart failure (HF) and preserved ejection fraction (HFpEF) display an increase in left ventricular (LV) filling pressure during activity that contributes to increased morbidity and mortality.[1–5] Elevated filling pressures in HFpEF may be caused by several mechanisms that may differ in various HFpEF phenotypes. The mechanisms may also differ in women, who outnumber men by a 2:1 ratio in this syndrome.

Obesity, as defined by body mass index (BMI), is a major risk factor for HFpEF, and the relationship is stronger in women.[6,7] Women display multiple differences in body composition and the distribution of fat that may be relevant to the development and progression of HFpEF. Visceral adipose tissue (VAT), defined as fat stored around internal organs, has been shown to be more harmful than fat stored in other depots.[8–11] Abdominal VAT functions as a metabolically active endocrine organ, secreting inflammatory and profibrotic mediators, which may directly or indirectly influence cardiac function and haemodynamics.[12,13] Visceral adipose tissue is greater in men than women, but recent data have revealed that for any increase in VAT, there is higher risk for the development of cardiometabolic disorders in women compared with men.[14] Fat mass increases markedly in women during the menopause transition, an interval after which the incidence of HFpEF rises dramatically.[15]

We hypothesized that sex-specific differences in VAT would differentially relate to haemodynamic indicators of disease severity in women as compared with men with HFpEF, with greater relationships in women, independent of total BMI. To test this hypothesis, we compared relationships between VAT and cardiac haemodynamics at rest and during exercise in women and men with and without HFpEF, matched for age and body mass.

Methods

Study population

The present study sought to evaluate two different but related questions. The first was whether the amount of VAT in women and men is differentially related to haemodynamic alterations that develop in HFpEF. The second question was whether the amount of VAT differed in women and men as compared with age-, sex-, and BMI-matched control subjects.

To address the first question, consecutive patients undergoing exercise right heart catheterization for the evaluation of unexplained dyspnoea at Mayo Clinic, Rochester, MN, from April 2007 to January 2018, were evaluated. From this cohort, we identified patients with invasively proven HFpEF with NYHA class II–III symptoms of dyspnoea, normal ejection fraction (EF; ≥50%), and elevated LV filling pressures [pulmonary capillary wedge pressure (PCWP) at rest >15 mmHg and/or with exercise ≥25 mmHg], fulfilling diagnostic criteria from the heart failure association (HFA) of the European Society of Cardiology (ESC).[16] From this group, patients with abdominal computed tomography (CT) examinations in a compensated (outpatient) state that were performed within 6 months from the date of catheterization were identified.

To address the second question, sex-, age-, and BMI-matched control subjects were identified from two sources. First, patients referred to invasive haemodynamic exercise testing during the same time period with no evidence of HF was found on catheterization were included if they also underwent abdominal CT within 6 months of assessment. In order to include an age-, sex-, and BMI-matched comparator population of equal sample size, we also included healthy volunteers participating in a bone health study derived from the Rochester Epidemiology Project[17] who underwent abdominal CT scanning as part of that protocol. A total of 34 women and 20 men were identified from this cohort allowing for the mean age and BMI distributions to be matched between control and HFpEF groups. Haemodynamic data were not available for the latter group but they were included in the comparisons of body composition. Plasma volume was calculated using the formula (1-haematocrit) × [a + (b × weight in kg)] where a = 1530 for men and 864 for women, and b = 41 for men and 47.9 for women.[18] Total blood volume was calculated as PV/(1-haematocrit).

Catheterization protocol

Subjects from the invasive cohort underwent symptom-limited supine cycle ergometry testing with simultaneous expired gas analysis as previously described.[19,20] Right heart catheterization was performed using a 9-Fr sheath via the right internal jugular vein. Right atrial pressure (RAP),

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pulmonary artery (PA) pressure, and PCWP were measured at end-expiration (mean of ≥3 beats) using 2-Fr high fidelity micromanometer-tipped catheters (Millar Instruments, Houston, TX, USA) advanced through the lumen of a 7-Fr fluid-filled catheter (Balloon wedge, Arrow). Transducers were zeroed at the mid-axilla, measured using laser callipers in each patient. The PCWP position was confirmed by appearance on fluoroscopy, characteristic pressure waveforms, and oximetry (saturation ≥94%). A 4–6 Fr radial arterial cannula was used to measure the arterial blood pressure and for sampling of the arterial blood gases throughout the study.

After baseline data were acquired, haemodynamic assessment and expired gas analysis were performed during the supine cycle ergometry exercise, starting at 20 W for 5 min followed by 10–20 W increments in workload (3-min stages) to subject-reported exhaustion. Pressure tracings were digitized (240 Hz) and analysed offline in a blinded fashion without knowledge of clinical characteristics or body size.

Measurement of adipose components

Abdominal CT scans were obtained according to clinical indications within 6 months of catheterization. A single slice at the level of the 3rd lumbar vertebra was manually identified and extracted in Digital Imaging and Communication in Medicine (DICOM) format. Measurements of visceral and subcutaneous fat areas and skeletal muscle area were then performed in a blinded fashion using previously validated semi-automated software for body composition analysis (BodyCompSlicer).[21] In brief, the software automatically identifies three boundary lines: one between the external air and subcutaneous fat (boundary 1); another between the subcutaneous fat and abdominal wall/paraspinal muscles (boundary 2); and a third between the abdominal wall/paraspinal muscles and visceral fat (boundary 3) (Supplementary material online, *Figure S1*). The boundaries are then manually corrected where necessary. Visceral adipose tissue area, subcutaneous adipose tissue area (SAT area), and skeletal muscle area (cm^2) are then calculated based upon the tomographic cross-sectional areas. Visceral adipose tissue area was defined as the area containing pixels within boundary 3 with attenuation value between -150 and -30 HU, excluding bowel content. Subcutaneous adipose tissue area was defined as the area containing pixels between boundaries 1 and 2 with an attenuation value of -190 to -30 HU.

Statistical analysis

Because there are important sex differences in body composition, the primary case-control comparisons were performed separately in women and men. Data are presented as mean (standard deviation, SD), median (interquartile range), or number (%). Between-group differences were compared using the unpaired *t*-test, Wilcoxon rank-sum test, and χ^2 or Fisher's exact test, as appropriate. Pearson correlation analysis was used to assess the relationships between continuous variables in each sex. Linear regression models with an interaction term were performed to test the sex differences on the association between central haemodynamics and VAT area. Univariable and multivariable linear regression models were used to assess the predictive value of VAT area. Moreover, we performed logistic regression analysis with the presence of HFpEF as a dependent variable. Pre-specified variables including age, hypertension, diabetes mellitus, and HFpEF were included in the multivariable models a priori, regardless of any associations in the univariate analysis, on the basis of our own hypothesis and previous findings.[10] In univariable and multivariable linear regression analyses, 95% confidence intervals were calculated. Given the mechanistic nature of these analyses, adjustment for multiple hypothesis testing was not performed. To further explore the impact of increased VAT on exercise haemodynamics, we categorized subjects into groups as normal or elevated VAT using VAT area of >126 cm^2 in women and >203 cm^2 in men to define elevated VAT. These values were determined from the distribution of healthy volunteers using VAT-area values >2 SD from the mean of normal weight healthy adults participating in the Rochester Epidemiology Project.[17] A two-sided *P*-value of <0.05 was considered statistically significant. All data were analysed using JMP14.0 (SAS Institute Inc., Cary, NC, USA) and SPSS version 25.0 (SPSS Inc., Chicago, IL, USA).

Results

Subject characteristics

A total of 105 HFpEF (42 male and 63 female) and 105 age-, sex-, and BMI-matched control subjects were evaluated (*Table 1*, *Figure 1*). Indications for abdominal CT imaging for the study patients are provided in the Supplementary material online, *Table S1*. Patients referred for CT imaging tended to be younger and displayed slightly lower haemoglobin, but other baseline characteristics were similar to patients not referred for CT (Supplementary material online, *Table S2*). As expected, women and men with HFpEF displayed lower haemoglobin and higher N-terminal-pro-brain natriuretic peptide (NT-proBNP) levels compared with control subjects (*Table 1*). The prevalence of hypertension tended to be higher in HFpEF women compared with control women, but there were no differences in the prevalence of known diabetes or fasting blood glucose levels. The prevalence of atrial fibrillation was higher in HFpEF in both sexes. As expected, use of diuretics and neurohormonal antagonists was higher in HFpEF compared with controls (*Table 1*). As compared with respective controls, both women and men with HFpEF displayed greater estimated plasma volume, despite higher diuretic use, and greater left atrial volumes. Left ventricular EF was slightly but significantly lower in women with HFpEF compared with control women (*Table 1*). Epicardial adipose tissue thickness was similar overall in the groups and was moderately correlated with VAT area ($r = 0.45$, $P < 0.0001$ for women, $r = 0.31$, $P = 0.01$ for men).

Sex-stratified differences in fat distribution

Overall, BMI was similar in women and men (31.8 ± 7.7 vs. 31.5 ± 6.6 kg/m^2, $P = 0.8$). Combing HFpEF and controls together, VAT area was 41% less in women than men (162 ± 97 vs. 274 ± 130 cm^2, $P < 0.0001$; Supplementary material online, *Table S3*). However, stratified case-control analyses revealed an important difference in the relationship between VAT area and HFpEF that differed by sex. Visceral adipose tissue area was significantly greater in women with HFpEF as compared with control women (186 ± 112 vs. 139 ± 72 cm^2, $P = 0.006$). This difference was maintained after indexing for other indices of general adiposity and body size (height, weight, and BMI; *Table 2*). *Figure 2* illustrates the differences in VAT area in control and HFpEF women despite similar BMI. Absolute SAT area was also higher (or tended to be higher) in women with HFpEF as compared with control women, but the differences were of lesser magnitude. In men, VAT area was not significantly different in HFpEF compared with control men before and after indexed body size, though there was a non-significant trend to higher VAT area in men with HFpEF (*Table 2*).

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Table 1 Baseline characteristics

	Control women (*n* = 63)	HFpEF women (*n* = 63)	*P*-value	Control men (*n* = 42)	HFpEF men (*n* = 42)	*P*-value
Age (years)	64 ± 14	64 ± 14	0.9	66 ± 14	66 ± 15	0.9
Body mass index (kg/m2)	31.1 ± 7.5	32.5 ± 7.9	0.3	31.3 ± 5.1	31.6 ± 7.9	0.8
Plasma volume (mL)	2853 ± 552	3283 ± 719	0.0007	3158 ± 501	3485 ± 695	0.02
Total blood volume (mL)	4532 ± 917	5020 ± 1135	0.01	5509 ± 823	5598 ± 1102	0.7
Comorbidities						
Hypertension	34 (54%)	44 (70%)	0.07	28 (67%)	29 (69%)	0.8
Diabetes mellitus	9 (14%)	14 (22%)	0.2	4 (9%)	8 (19%)	0.2
Atrial fibrillation	2 (3%)	17 (27%)	0.0003	2 (5%)	12 (29%)	0.007
Pacing device	1 (2%)	13 (21%)	0.001	5 (12%)	5 (12%)	1.0
Medications						
Beta-blocker	25 (40%)	33 (52%)	0.2	9 (21%)	25 (60%)	0.0003
ACEI/ARB	8 (13%)	23 (37%)	0.002	12 (25%)	24 (57%)	0.008
Loop diuretic	5 (8%)	28 (44%)	0.0001	4 (10%)	16 (38%)	0.004
MRA	4 (6%)	13 (21%)	0.03	2 (5%)	5 (12%)	0.4
Thiazide	8 (13%)	5 (8%)	0.6	7 (17%)	2 (5%)	0.16
Laboratories						
Haemoglobin (g/dL)	12.4 ± 1.3	11.5 ± 1.5	0.0008	14.2 ± 1.6	12.5 ± 1.8	<0.0001
Estimated GFR (mL/min/1.73m2)	60 ± 18	62 ± 21	0.5	64 ± 16	59 ± 24	0.3
Fasting glucose (mg/dL)	100 (93, 119)	99 (91, 117)	0.5	100 (93, 113)	104 (96, 130)	0.1
NT-proBNP (pg/mL)[a]	89 (51, 380)	290 (91, 1099)	0.01	111 (29, 340)	728 (48, 1713)	0.002
Sinus rhythm	89 (51, 380)	201 (72, 491)	0.1	111 (37, 302)	513 (172, 1068)	0.03
Atrial fibrillation	—	1292 (601, 1719)	—	199 (15, 383)	1619 (728, 2344)	0.049
NT-proBNP > 125 pg/mL, *n* (%)[a]	7 (39)	39 (68)	0.03	6 (43)	25 (83)	0.007
Sinus rhythm	7 (39)	25 (61)	0.1	5 (42)	17 (81)	0.02
Atrial fibrillation	0 (0)	14 (88)	<0.0001	1 (8)	8 (89)	0.2
Estimated plasma volume (mL)	2853 ± 551	3279 ± 713	0.0007	3157 ± 501	3484 ± 695	0.02
Echocardiography						
LV mass index (g/m2.7)	37.3 (30.0, 50.5)	40.5 (33.2, 50.3)	0.3	42.4 (35.2, 49.7)	43.2 (33.4, 53.1)	0.7
Ejection fraction (%)	66 ± 4	63 ± 5	0.003	60 ± 7	61 ± 6	0.5
E/e′ ratio	10 (7, 14)	12 (8, 16)	0.07	9 (8, 14)	11 (8, 17)	0.3
LA volume index (mL/m2)	29 (21, 34)	34 (29, 39)	0.007	29 (25, 33)	35 (26, 51)	0.04
Epicardial fat thickness (mm)	5.1 ± 2.5	5.6 ± 3.4	0.4	4.7 ± 2.7	5.0 ± 3.4	0.7

Values are mean ± SD, median (interquartile range), or *n* (%).
ACEI/ARB, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; GFR, glomerular filtration rate; HFpEF, heart failure with preserved ejection fraction; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal-pro-Brain Natriuretic Peptide.
[a]Available for *n* = 119 (18/57/14/30 for control/HFpEF women and control/HFpEF men, respectfully).

In linear regression analysis, BMI, diabetes, and HFpEF diagnosis were each associated with VAT area among women (*Table 3*). Among men, BMI and hypertension were associated with VAT area, but HFpEF status was not. Importantly, the presence of HFpEF was independently associated with VAT area in women even after incorporating age, BMI, hypertension, and diabetes status into the multivariable model, but there was no statistically significant relationship observed in men (*Table 3*).

Differential relationships between visceral adipose tissue and haemodynamics in women

A total of 105 HFpEF (*n* = 63 women) and 51 control subjects (*n* = 29 women) underwent invasive haemodynamic exercise testing (*Table 4*). As expected based upon group definitions, compared with their respective controls, both HFpEF women and men displayed higher RAP, PA pressures, and PCWP, at rest and during exercise, and lower peak workload achieved. There were no differences in resting or exercise haemodynamics comparing women and men with HFpEF (Supplementary material online, *Table S5*).

At baseline, prior to exercise, VAT area was modestly correlated with RAP, PA mean pressure, and PCWP in women, but not in men (Supplementary material online, *Table S6*). These differences were amplified during exercise, where increasing VAT area was more strongly correlated with exercise haemodynamics, but this relationship was again restricted to women and not observed in men, with significant sex–VAT interactions observed for exercise PCWP and RAP (*Figure 3A*, Supplementary material online, *Figure S2*) as well as

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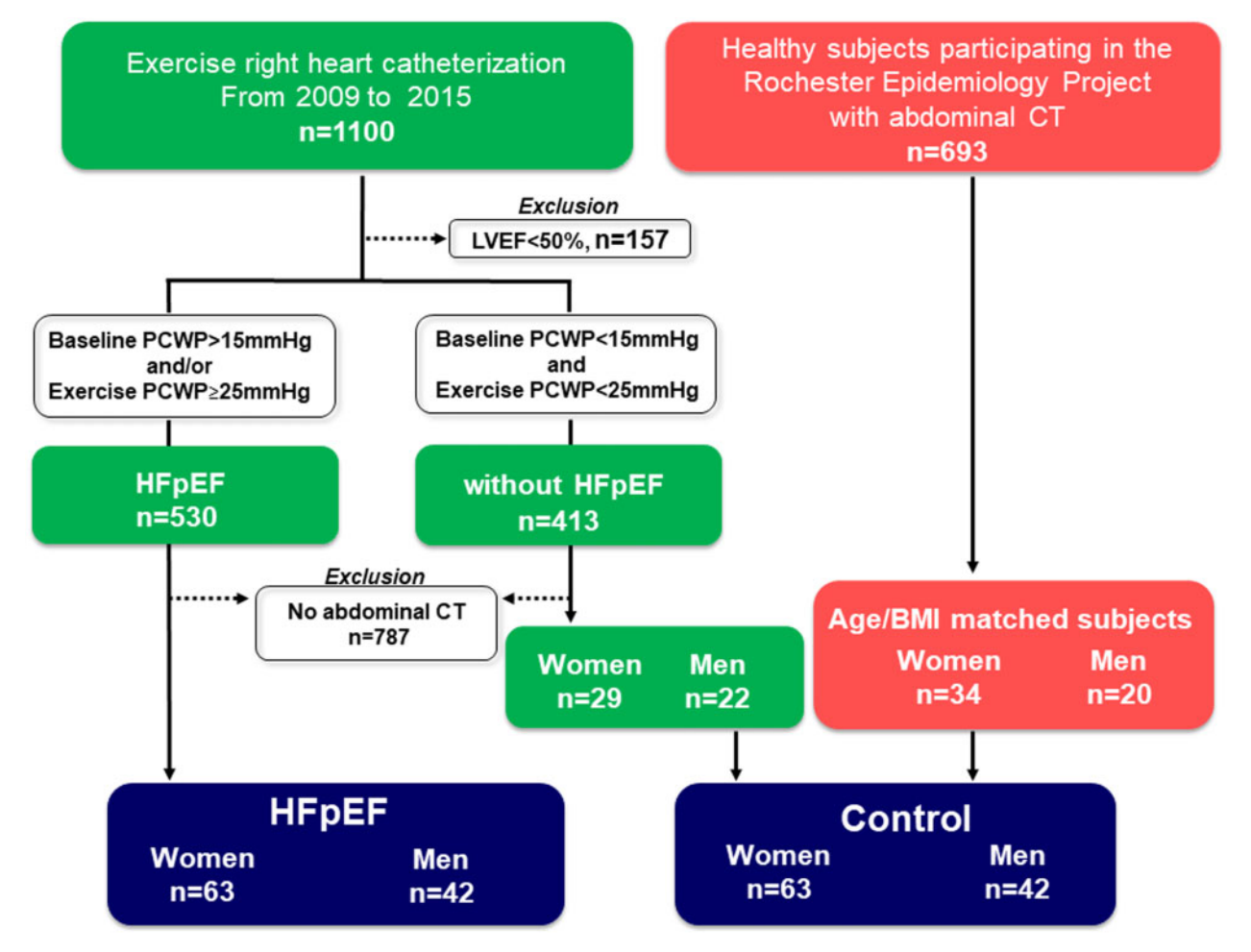

Figure 1 Patient selection. In 1100 patients referred for exercise right heart catheterization with preserved left ventricular ejection fraction, 530 had heart failure with preserved ejection fraction, of whom 105 underwent abdominal computed tomography imaging, including 63 women. Control subjects were identified from 51patients referred to invasive haemodynamic exercise testing with no evidence of heart failure who underwent abdominal computed tomography, and 54 healthy subjects participating in the Rochester Epidemiology Project. BMI, body mass index; CT, computed tomography; HFpEF, heart failure with preserved ejection fraction; LVEF, left ventricular ejection fraction; PCWP, pulmonary capillary wedge pressure.

Table 2 Abdominal fat distribution

	Control women ($n = 63$)	HFpEF women ($n = 63$)	*P*-value	Control men ($n = 42$)	HFpEF men ($n = 42$)	*P*-value
VAT area (cm^2)	139 ± 72	186 ± 112	0.006	252 ± 92	294 ± 158	0.1
Height-indexed VAT (cm^2/m^2)	50 ± 27	70 ± 42	0.01	82 ± 29	93 ± 49	0.2
Weight-indexed VAT (cm^2/kg)	1.6 ± 0.7	2.0 ± 1.1	0.01	2.6 ± 0.8	2.8 ± 1.2	0.4
BMI-indexed VAT (cm^2*m^2/kg)	4.3 ± 2.0	5.4 ± 2.8	0.007	8.0 ± 2.5	9.0 ± 4.0	0.2
SAT area (cm^2)	258 ± 114	314 ± 163	0.03	215 ± 121	253 ± 149	0.2
Height-indexed SAT (cm^2/m^2)	99 ± 44	117 ± 59	0.05	69 ± 36	79 ± 47	0.1
Weight-indexed SAT (m^2/kg)	3.1 ± 1.0	3.5 ± 1.2	0.05	2.1 ± 0.7	2.4 ± 0.9	0.2
BMI-indexed SAT (m^2*m^2/kg)	8.0 ± 2.6	9.2 ± 3.2	0.03	6.6 ± 2.5	7.5 ± 3.1	0.1

Values are mean ± SD, median (interquartile range), or *n* (%).
BMI, body mass index; HFpEF, heart failure with preserved ejection fraction; SAT, subcutaneous adipose tissue; VAT, visceral adipose tissue.

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exercise PA pressures (Supplementary material online, *Table S6*). These interactions remained significantly after adjusting for use of mineralocorticoid receptor antagonists.

Exercise PCWP was strongly correlated with estimated plasma volume in women, but not in men (interaction $P = 0.002$, Supplementary material online, *Figure S3*). Similar sex differences were observed evaluating total blood volume and exercise PCWP, which were significantly correlated in women ($r = 0.45$, $P < 0.0001$) but not men ($r = -0.10$, $P = 0.40$, sex interaction $P = 0.0004$). Linear regression analysis revealed that RAP and PCWP during exercise were higher with increasing VAT area in women but not men. In linear regression, there was a 4.0 mmHg increase in exercise PCWP for every 100 cm^2 increase in VAT area in women (95% CI 2.1, 6.0 mmHg; $P < 0.0001$), but no significant relationship was observed in men (*Figure 3B*). Similar sexual dimorphisms in the correlations with VAT area were observed for RAP and PA pressure (Supplementary material online, *Table S7*).

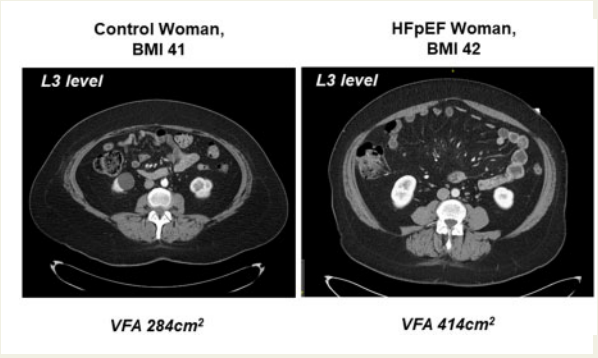

Figure 2 Abdominal computed tomography image of control and heart failure with preserved ejection fraction women. Example imaging results from an obese woman with heart failure with preserved ejection fraction (right panel) and a control woman of similar body mass index (left panel). BMI, body mass index; CT, computed tomography; HFpEF, heart failure with preserved ejection fraction; LVEF, left ventricular ejection fraction; PCWP, pulmonary capillary wedge pressure.

Impact of excess visceral adipose tissue in women and men independent of heart failure

To further explore how VAT impacts haemodynamics in women and men independent of HF status, all men and women (case and control) were combined together and separated into groups based upon the presence or absence of increased VAT. Increased VAT was defined by values >126 cm^2 in women or >203 cm^2 in men, which correspond to VAT area values >2 SD from the mean of normal weight healthy women and men. In women, the presence of excess VAT was associated with a 33% higher exercise PCWP as compared with women without excess VAT (*Figure 4*), whereas there was no difference in exercise PCWP comparing men with and without excess VAT (*Table 5*). The same pattern was also observed for RAP and PA pressure during exercise in women and men.

Discussion

In this study, we aimed to better understand how sex influences the relationships between central obesity quantified by VAT and the haemodynamics derangements that cause symptoms in patients with HFpEF. We demonstrate that VAT area measured using CT was significantly greater in women with HFpEF when compared with women of similar age and BMI. In linear regression analyses, VAT area was independently associated with the presence of HFpEF in women but not men. In addition to the greater quantity of VAT present in women with HFpEF compared with control women, we observed important qualitative differences in the associations between VAT and haemodynamics by sex. Exercise haemodynamics were equally abnormal in women and men with HFpEF, but excess VAT was only associated with haemodynamic derangements in women, and not in

Table 3 Correlates of visceral adipose tissue area by linear regression analyses

Women	**Univariable model**			**Multivariable model ($R^2 = 0.54$)**			
	β	**95%CI**	***P*-value**	**β**	**95%CI**	***P*-value**	**VIF**
Age (years)	0.87	(-0.39, 2.13)	0.2	0.90	(-0.04, 1.85)	0.06	1.2
BMI (kg/m^2)	8.89	(7.32, 10.5)	<0.0001	8.56	(7.01, 10.1)	<0.0001	1.0
Hypertension	8.55	(-26.7, 43.8)	0.6	-14.1	(-40.4, 12.1)	0.3	1.2
Diabetes mellitus	53.3	(9.94, 96.6)	0.02	13.7	(-17.6, 44.9)	0.4	1.1
HFpEF	47.3	(14.1, 80.5)	0.006	36.0	(12.2, 59.8)	0.003	1.0
Men	**Univariable model**			**Multivariable model ($R^2 = 0.52$)**			
	β	**95%CI**	***P*-value**	***β***	**95%CI**	***P*-value**	**VIF**
Age (years)	2.23	(0.34, 4.23)	0.07	3.03	(1.60, 4.45)	<0.0001	1.1
BMI (kg/m^2)	12.3	(8.91, 15.6)	<0.0001	12.7	(9.66, 15.8)	<0.0001	1.1
Hypertension	79.4	(21.0, 137.8)	0.008	35.5	(-8.07, 79.0)	0.1	1.1
Diabetes mellitus	41.2	(-39.6, 121.9)	0.3	5.7	(-51.8, 63.1)	0.8	1.1
HFpEF	41.5	(-14.7, 97.6)	0.1	37.0	(-2.57, 76.6)	0.07	1.1

ACEI/ARB, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; CI, confidence interval; GFR, glomerular filtration rate; HFpEF, heart failure with preserved ejection fraction; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal-pro-Brain Natriuretic Peptide; VIF, variance inflation factor.

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Table 4 Haemodynamics in control and heart failure with preserved ejection fraction subjects by sex

	Control women ($n = 29$)	HFpEF women ($n = 63$)	*P*-value	Control men ($n = 22$)	HFpEF men ($n = 42$)	*P*-value
Baseline haemodynamics						
Heart rate (b.p.m.)	73 ± 15	70 ± 14	0.4	64 ± 13	68 ± 13	0.3
Systolic blood pressure (mmHg)	149 ± 19	145 ± 27	0.4	151 ± 18	142 ± 24	0.1
RA pressure (mmHg)	5 ± 2	10 ± 5	<0.001	6 ± 3	10 ± 4	0.001
PA systolic pressure (mmHg)	27 ± 7	41 ± 12	<0.001	30 ± 6	42 ± 14	<0.001
PA mean pressure (mmHg)	17 ± 4	27 ± 8	<0.001	18 ± 4	27 ± 9	<0.001
PCWP (mmHg)	9 ± 3	16 ± 5	<0.001	9 ± 3	16 ± 5	<0.001
Exercise haemodynamics						
Work load (Watts)	40 (20, 80)	20 (20, 60)	0.06	80 (40, 100)	40 (20, 60)	0.002
Heart rate (b.p.m.)	128 ± 19	107 ± 20	0.004	107 ± 21	97 ± 17	0.2
Systolic blood pressure (mmHg)	177 ± 37	177 ± 31	1.0	188 ± 25	172 ± 31	0.046
RA pressure (mmHg)	8 ± 4	19 ± 8	<0.001	11 ± 4	20 ± 5	<0.0001
PA systolic pressure (mmHg)	41 ± 13	63 ± 16	<0.001	49 ± 12	63 ± 16	0.0007
PA mean pressure (mmHg)	27 ± 8	44 ± 11	<0.001	31 ± 7	43 ± 9	<0.0001
PCWP (mmHg)	13 ± 5	31 ± 7	<0.001	16 ± 5	29 ± 5	<0.0001

Values are mean ± SD, median (interquartile range).
ACEI/ARB, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; GFR, glomerular filtration rate; HFpEF, heart failure with preserved ejection fraction; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal-pro-Brain Natriuretic Peptide; PA, pulmonary arterial; PCWP, pulmonary capillary wedge pressure.

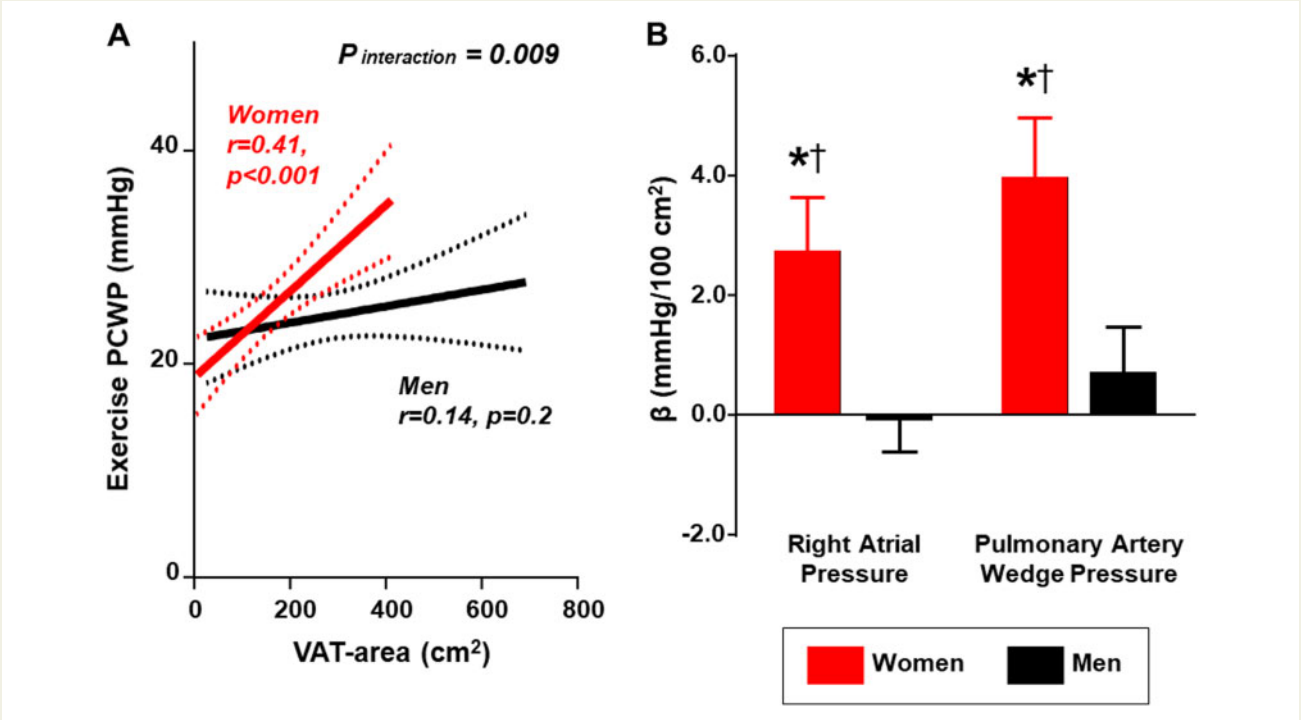

Figure 3 Relationships between exercise central haemodynamics and visceral adipose tissue area. (*A*) Elevation in pulmonary capillary wedge pressure was related to increase in visceral fat area in women, but not men. (*B*) Parameter estimates from linear regression for the change in exercise right atrial pressure and pulmonary capillary wedge pressure with increasing visceral adipose tissue in women and men. There was a 4 mmHg increase in exercise pulmonary capillary wedge pressure for every 100 cm^2 increase in VAT area in women, but no significant relationship was seen in men. *Sex–VAT interaction $P < 0.05$. †Sex–VAT interaction after adjusting for BMI $P < 0.05$. BMI, body mass index; CT, computed tomography; HFpEF, heart failure with preserved ejection fraction; LVEF, left ventricular ejection fraction; PCWP, pulmonary capillary wedge pressure.

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men. Combining cases and controls together in a separate analysis confirmed that excess VAT is uniquely associated with abnormal exercise haemodynamics in women, independent of HF status. These data demonstrate for the first time an important sexual dimorphism in the biologic relationships between adipose tissue distribution and haemodynamic abnormalities that cause disability in HFpEF, pointing to an important role for visceral fat in women with HFpEF.

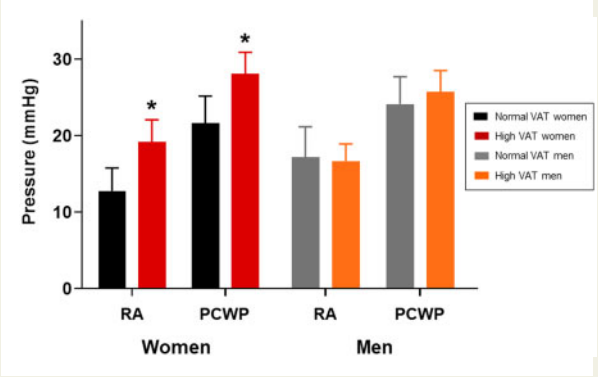

Figure 4 Comparison of the exercise haemodynamics between high visceral adipose tissue and normal visceral adipose tissue based on gender. High visceral adipose tissue was defined as >126 cm^2 in women and >203 cm^2 in men based upon the 95th percentile of a normal cohort. In women, the presence of high visceral adipose tissue was associated with a 33% greater exercise pulmonary capillary wedge pressure as compared with women without excess visceral adipose tissue, whereas there was no difference in exercise pulmonary capillary wedge pressure comparing men with and without excess visceral adipose tissue. The same pattern was also observed for right atrial pressure during exercise in women and men. *$P < 0.05$ vs. normal visceral adipose tissue women. BMI, body mass index; CT, computed tomography; HFpEF, heart failure with preserved ejection fraction; LVEF, left ventricular ejection fraction; PCWP, pulmonary capillary wedge pressure; RAP, right atrial pressure.

Sex difference in adipose tissue and its relationship with heart failure with preserved ejection fraction

Obesity is an independent risk factor for HFpEF.[6] Risk appears to be even greater with increasing amounts of VAT,[22] and in women as compared with men.[6] The mere presence of obesity in a patient with dyspnoea increases the odds of HFpEF more than three-fold.[23] Increase in body fat causes haemodynamic, metabolic, inflammatory, and hormonal perturbations that stress the heart and vasculature.[24] Body mass index forms the basis for the WHO definition of obesity and is a useful and easily measurable surrogate of overall adiposity.[25] However, this measure grossly oversimplifies the heterogeneity of body fat composition.[26] Varying distributions of body fat are associated with differential metabolic risk, and VAT in particular is most closely linked to cardiometabolic abnormalities.[10,27,28] Moreover, independent of BMI, VAT is an important predictor of early cardiac dysfunction[29,30] and even frank HF.[8,31,32] However, the mechanisms underlying the greater risk of HFpEF with increasing adipose burden in women have remained unclear.[6,30]

It is well-known that VAT is higher in men than women, as confirmed in the present study. However, when comparing women with HFpEF to age- and BMI-matched women without HF, we observed significant increases in absolute VAT that would not have otherwise been apparent combining the sexes together. Importantly, the amount of VAT was related to haemodynamic derangements indicative of HFpEF severity in women but not men. These data may help to explain the recent observation that excess VAT is associated with development of incident HFpEF but not heart failure with reduced ejection fraction (HFrEF),[22] and that women have greater risk of HFpEF with increasing BMI as compared with men.[6] The incidence of HFpEF rises strikingly with age in women, particularly after menopause, and recent longitudinal studies have revealed that the menopause transition is associated with an increase in fat mass[15] that parallels an increased risk of HF.[33] The current data, in tandem with these prior epidemiologic studies, strongly support an important role for VAT in the pathophysiology of HFpEF in women.

Table 5 Haemodynamics stratified by visceral adipose tissue and sex

	Normal VAT women ($n = 40$)	High VAT women ($n = 52$)	*P*-value	Normal VAT men ($n = 17$)	High VAT men ($n = 47$)	*P*-value
Baseline haemodynamics						
RA pressure (mmHg)	7 ± 5	10 ± 5	0.02	9 ± 5	8 ± 4	0.5
PA mean pressure (mmHg)	22 ± 10	25 ± 7	0.10	28 ± 13	22 ± 6	0.02
PCWP (mmHg)	13 ± 6	15 ± 6	0.09	14 ± 7	13 ± 5	0.5
Exercise haemodynamics						
RA pressure (mmHg)	12 ± 8	19 ± 8	<0.001	17 ± 8	16 ± 6	0.7
PA mean pressure (mmHg)	35 ± 14	41 ± 12	0.03	42 ± 11	38 ± 10	0.17
PCWP (mmHg)	21 ± 10	28 ± 10	0.001	25 ± 6	24 ± 9	0.9

Values are mean ± SD, median (interquartile range).
ACEI/ARB, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; GFR, glomerular filtration rate; HFpEF, heart failure with preserved ejection fraction; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal-pro-Brain Natriuretic Peptide; PA, pulmonary arterial; PCWP, pulmonary capillary wedge pressure.

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Potential mechanisms of sex-specific visceral adipose tissue interaction

Increases in VAT are associated with greater risk of cardiometabolic disorders such as hypertension, coronary disease, and diabetes in both sexes, but the magnitude of risk increase is much greater in women.[14] In a recent Mendelian randomization analysis conducted from the UK Biobank cohort, Karlsson *et al.* demonstrated a large sex difference in causal effect between VAT and the risk of diabetes, with an odds ratio of 2.50 (95% CI, 1.98–3.14) in men and 7.34 (95% CI, 4.48–12.0) in women.

Adipose tissue, particularly the dysfunctional fat observed in people with central obesity, secretes leptin, neprilysin, and aldosterone,[34,35] which may cause sodium retention and plasma volume expansion. A potential role for greater volume overload in women is supported by the stronger correlations between VAT and estimated plasma volume and total blood volume in women in the current study, and the steeper increase in exercise PCWP with higher plasma and blood volume that was only observed in women and not men. Further study is required using more direct measures of blood and plasma volume to explore this further.[36]

Adipokines secreted by VAT may also result in adipose tissue inflammation, microvascular dysfunction, and myocardial fibrosis, all of which have been implicated in the pathophysiology of HFpEF.[12,34] An animal study has suggested that VAT produces a number of profibrotic mediators that activate TGF-beta signalling cascades and promote chronic cardiac remodelling.[13,37] In humans, it is known that VAT correlates strongly with inflammation and oxidative stress.[9]Population-based studies have suggested a distinct inflammatory and adipokine profile in women as compared with men for a given BMI,[38,39] and it is possible that this may be mediated by sex-specific differences in VAT regardless of absolute BMI. Women also display differences in myocardial metabolism and substrate utilization that may render them more vulnerable to the deleterious effects of excess VAT and its associated metabolic sequelae.[40]

An increase in VAT may also be associated with increases in plasma volume or intra-abdominal pressure that may contribute to extrinsic restraint on the heart across the diaphragm, and this would be expected to increase during exercise when venous return is augmented.[41,42] The positive correlation with increases in both RA and PCWP and VAT supports a potential role for extrinsic restraint in the pathogenesis of VAT mediated haemodynamic derangements in women with HFpEF.[43] It may be that women with smaller average heights may be more predisposed to the haemodynamic mass effect of VAT compared with men.

Clinical implications

In the PARAGON-HF trial, a subgroup analysis demonstrated that women responded more favourably to sacubitril-valsartan than men.[44] If women with HFpEF display greater volume expansion and more abnormal haemodynamic severity of disease due to increased neprilysin activity from relatively greater VAT, this may partially explain the differential benefit by sex observed in PARAGON. In addition, a *post-hoc* analysis of the TOPCAT Trial suggested that spironolactone therapy reduced all-cause mortality in women with HFpEF but not men.[45] This may be related to the antifibrotic actions of spironolactone in a cohort at high risk for cardiac remodelling from VAT, in combination with its diuretic effects.

Ultimately, targeting VAT with dietary, drug, and surgical weight loss strategies would be the most direct therapeutic strategy to consider in this population. In patients without HF, weight loss is associated with reductions in left- and right-sided filling pressures, with trend for reduction in plasma volume.[24] In the only randomized trial of weight loss in HFpEF, nearly 80% of participants were women and favourable effects were observed on exercise performance and quality of life, with highly significant reductions in VAT.[46] The results of our study suggest that women with HFpEF in particular stand to benefit from weight loss interventions, particularly when targeting VAT, and this may improve haemodynamic derangements with activity.

Limitations

This is a single-centre study from a tertiary referral centre, and participants were required by design to have been referred for abdominal CT imaging, which introduces selection and referral bias. The mean age of the HFpEF patients included is somewhat lower than some trial cohorts,[44] but similar to others,[47] and this should be considered when applying the current results to other populations. Plasma volume was estimated and not directly measured. The cross-sectional nature of the study limits the ability to make inferences regarding causality. Data on cardiometabolic hormones and inflammatory mediators, such as aldosterone, leptin, or neprilysin, were not measured. However, assessments of both VAT and haemodynamics were made using robust, gold standard methods, and the combination of both assessments in the same patients, with appropriately matched non-HF comparator patients is unique in literature and represents a significant strength of the current analysis.

Conclusions

Heart failure with preserved ejection fraction in women is characterized by an excess of VAT, even after accounting for age, sex, and total adiposity using BMI, while similar relationships were not observed in men. These data indicate that an overabundance of VAT may be more pathologic in women as compared with men. The present study provides new insights into the role of visceral fat in the development and progression of HFpEF in women that may partially explain their greater susceptibility to HFpEF with increasing BMI. Further study is warranted to better understand the factors that mediate the relationships between VAT and HFpEF in women, and to explore how these processes may be targeted to mitigate or prevent disease progression.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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