

Epicardial adipose tissue and pericardial constraint in heart failure with preserved ejection fraction

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Abstract

Aims Obesity and epicardial adiposity play a role in the pathophysiology of heart failure with preserved ejection fraction (HFpEF), and both are associated with increased filling pressures and reduced exercise capacity. The haemodynamic basis for these observations remains inaccurately defined. We hypothesize that an abundance of epicardial adipose tissue (EAT) within the pericardial sac is associated with haemodynamic signs of pericardial constraint.

Methods and results HFpEF patients who underwent invasive heart catheterization with simultaneous echocardiography were included. Right atrial pressure (RAP), right ventricular end-diastolic pressure, and pulmonary capillary wedge pressure (PCWP) were invasively measured. The presence of a square root sign on the right ventricular pressure waveform and the RAP/PCWP ratio (surrogate parameters for pericardial constraint) were investigated. EAT thickness alongside the right ventricle was measured on echocardiography. Sixty-four patients were studied, with a mean age of 73 ± 10 years, 64% women, and a mean body mass index (BMI) of 28.6 ± 5.4 kg/m². In total, 47 patients (73%) had a square root sign. The presence of a square root sign was associated with higher BMI (29.3 vs. 26.7 kg/m², $P = 0.02$), higher EAT (4.0 vs. 3.4 mm, $P = 0.03$), and higher RAP (9 vs. 6 mmHg, $P = 0.04$). Women had more EAT than men (4.1 vs. 3.5 mm, $P = 0.04$), despite a comparable BMI. Women with a square root sign had significantly higher EAT (4.3 vs. 3.3 mm, $P = 0.02$), a higher mean RAP (9 vs. 5 mmHg, $P = 0.02$), and a higher RAP/PCWP ratio (0.52 vs. 0.26 , $P = 0.002$). In men, such associations were not seen, although there was no significant interaction between men and women ($P > 0.05$ for all analyses).

Conclusions Obesity and epicardial adiposity are associated with haemodynamic signs of pericardial constraint in patients with HFpEF. The pathophysiological and therapeutic implications of this finding need further study.

Keywords HFpEF; Epicardial adipose tissue; Invasive haemodynamics; Pericardial constraint

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Introduction

Obesity and epicardial adiposity in particular are increasingly suggested to play an important role in the pathophysiology of heart failure (HF) with preserved ejection fraction (HFpEF).^{1–3} It was recently shown that increased epicardial adipose tissue (EAT) was associated with incident HFpEF but not with incident HF with reduced ejection fraction.⁴ Furthermore, in patients with HFpEF, a higher amount of EAT was associated with a higher presence of atrial fibrillation, reduced exercise capacity, and an increased risk for HF hospitalization and mortality.^{5–8} However, the exact pathophysiological

mechanisms that underlie these associations remain inaccurately defined.

Borlaug and colleagues have shown that obesity-related HFpEF is characterized by a unique haemodynamic profile consisting of more volume overload, higher ventricular filling pressures, and greater ventricular interdependency.⁹ Recently, it was demonstrated that increased EAT in particular was associated with higher cardiac filling pressures and ventricular interdependence in HFpEF, independent of overall obesity.^{5,8} It can be speculated that the myocardium and the surrounding adipose tissue compete for space within the pericardial sac, and this hypothesis may potentially

explain the observation that especially an abundance of EAT was associated with higher filling pressures and exercise intolerance in HFpEF. However, an alternative hypothesis suggests that proinflammatory and profibrotic products of EAT may directly infiltrate into the myocardium, potentially leading to myocardial stiffness, diastolic dysfunction, and increased cardiac filling pressure, mimicking a restrictive-like cardiomyopathy.¹

In order to investigate whether an abundance of EAT is associated with pericardial constraint, we examined patients with HFpEF who underwent invasive heart catheterization with simultaneous echocardiography and studied the association between increased EAT, invasive filling pressures, and haemodynamic signs of pericardial constraint.

Methods

The present study population is a subset of a cohort of 102 outpatients with symptomatic HF with New York Heart Association functional class II or III, with a left ventricular (LV) ejection fraction > 45%, who were referred for routine right- and left-sided heart catheterization with simultaneous echocardiography.^{10,11} Additional inclusion criteria for the current study were the presence of structural and/or functional abnormalities of the left ventricle (i.e. $E/e' \geq 13$, mean e' septal and lateral wall < 9 cm/s, left atrial volume index ≥ 34 mL/m², left atrial parasternal diameter ≥ 45 mm, and/or N-terminal pro-brain natriuretic peptide ≥ 125 ng/L). Patients were excluded if echocardiography was not performed simultaneously with the invasive heart catheterization or if echocardiographic quality was insufficient for the assessment of the right ventricular (RV)-free wall and/or EAT alongside the RV wall. Patients with haemodynamically significant left-sided valvular heart disease were excluded as well. Only patients with the availability of the RV pressure waveform tracings were subsequently advanced into the present study population. This study was conducted in accordance with local and national regulations regarding retrospective clinical research, as verified and confirmed by the Institutional Review Board of the University Medical Center Groningen.

Heart catheterization protocol

All right and left heart catheterizations were performed in supine position by a single experienced cardiologist (E. S. H.), according to a standard protocol as previously described.^{10,11} All patients remained on their chronic medication, and none of the patients were on pulmonary vasodilators. A 7 F balloon-tipped catheter was inserted through the femoral vein, advanced into the right heart, and subsequently positioned in the pulmonary artery and wedge position. The

pulmonary capillary wedge pressure (PCWP), pulmonary artery pressure (PAP), RV end-diastolic pressure (RVEDP), and right atrial pressure (RAP) were recorded at end-expiration during normal breathing. Cardiac output was measured using the indirect Fick method and indexed for body surface area. Pulmonary vascular resistance (PVR) and stroke volume were calculated using the standard formulas. To control for pericardial pressure, the RAP/PCWP ratio was subsequently calculated.

The presence of a square root sign on the RV pressure waveform, which is a typical sign suggestive of pericardial constraint,¹² was scored by two independent reviewers (Y. C. and E. S. H.) for each patient using the digitally stored RV pressure waveforms. The study population was further dichotomized according to the presence or absence of the square root sign.

Left-sided heart catheterization was performed to exclude haemodynamically significant left-sided valve disease and significant coronary artery disease and to record LV end-diastolic pressure (LVEDP).

Echocardiographic protocol

All echocardiographic images were acquired simultaneously with the invasive heart catheterization using a Vivid S6 system (General Electric, Horton, Norway) and were digitally stored for offline analyses using EchoPAC (Version BT12). The echocardiographic protocol was previously described in detail.^{10,13} In brief, all echocardiographic parameters were assessed according to the current recommendations of the European Association of Cardiovascular Imaging and the American Society of Echocardiography¹⁴ and included LV ejection fraction, LV diastolic function (E , A , E/A ratio, LV septal and lateral wall e' , and E/e'), tricuspid annular plane systolic excursion, and RV lateral wall e' . The LV lateral e' and LV septal e' ratio and RV lateral e' and LV septal e' ratio were calculated.

EAT thickness alongside the RV-free wall was measured on the parasternal long and short axes. At the end of systole, the thickness of EAT was measured and expressed in millimetres. The measurement spanned two cardiac cycles, both at the end of systole, and the average of these two measurements was calculated.¹³

Statistical analysis

Data were presented as mean $\pm$ standard deviation, number (percentage), or median [interquartile range], according to distribution. Differences in continuous variables between two groups were compared using the independent sample t -test or the Mann–Whitney U test. Differences in categorical variables between two groups were performed using the χ^2

test or Fisher's exact test. For the comparison between two continuous variables, the Pearson correlation coefficient was used. Interaction analyses for the associations with sex were performed. A *P*-value of <0.05 was considered statistically significant. All data were analysed using SPSS Version 23 (IBM, Armonk, NY, USA).

Results

Of the initial 102 patients, 101 fulfilled the additional inclusion criteria. Four patients were excluded because the echocardiography was not performed simultaneously with the

heart catheterization. Furthermore, 22 patients had insufficient echocardiographic quality to assess EAT thickness alongside the RV-free wall. In another 11 patients, the RV pressure waveforms were not available for evaluating the square root sign. This left a final study sample of 64 patients with HFpEF, of which 41 (64%) were women. In total, 47 patients (73%) had a square root sign on the RV pressure waveform. The patient's characteristics of the entire study population, separated by the absence or presence of a square root sign, are detailed in *Table 1*. Most of the patients' characteristics were comparable between patients with and without a square root sign. However, body mass index (BMI) was significantly higher in patients with a square root sign.

Table 1 Baseline characteristics of the study population

	Total population (n = 64)	No square root sign (n = 17)	Square root sign (n = 47)	P-value
Age, years	73 ± 10	74 ± 11	73 ± 9	0.7
Sex, female	41 (64)	8 (47)	33 (70)	0.09
Body mass index, kg/m ²	28.6 ± 6	26.7 ± 2.6	29.3 ± 5.9	0.02
Vital signs				
Heart rate, b.p.m.	71 ± 12	75 ± 12	71 ± 13	0.9
Systolic blood pressure, mmHg	149 ± 25	158 ± 20	151 ± 27	0.3
Diastolic blood pressure, mmHg	69 ± 13	68 ± 13	71 ± 13	0.7
Comorbidities				
Systemic hypertension	42 (66)	10 (59)	32 (68)	0.5
Atrial fibrillation	36 (56)	9 (52)	27 (57)	0.7
Coronary artery disease	24 (38)	7 (41)	17 (36)	0.7
Diabetes mellitus	22 (34)	7 (41)	19 (40)	0.9

Variables are depicted as number (percentage), mean ± standard deviation, or median [interquartile range].

Table 2 Echocardiography and right heart catheterization

	Total population (n = 64)	No square root sign (n = 17)	Square root sign (n = 47)	P-value
Echocardiography				
LV ejection fraction, %	54 ± 6	56 ± 7	57 ± 4	0.6
E/e'	15 ± 8	20 ± 11	14 ± 6	0.07
LV e' lateral wall, cm/s	9.3 ± 3.8	8.2 ± 2.7	9.7 ± 4.1	0.2
LV e' septal wall, cm/s	6.8 ± 2.9	5.4 ± 2.2	7.4 ± 3.0	0.02
LV lateral/septal e' ratio	1.44 ± 0.45	1.62 ± 0.43	1.37 ± 0.45	0.07
RV lateral e', cm/s	11.1 ± 4.4	10.3 ± 3.8	11.4 ± 4.7	0.4
RV lateral/LV septal e'	1.74 ± 0.69	2.07 ± 0.89	1.61 ± 0.57	0.07
Left atrial volume index, mL/m ²	47 ± 15	48 ± 19	48 ± 14	0.9
TAPSE, mm	20 ± 5	20 ± 4	20 ± 5	0.9
Epicardial adipose tissue, mm	3.9 ± 1.4	3.4 ± 0.8	4.0 ± 1.4	0.03
Moderate to severe TR	19 (30%)	7 (41%)	12 (26%)	0.2
Invasive haemodynamics				
Mean RAP, mmHg	8 ± 4	6 ± 3	9 ± 5	0.04
RVEDP, mmHg	9 ± 4	8 ± 3	10 ± 4	0.2
Mean PAP, mmHg	32 ± 9	33 ± 11	31 ± 9	0.5
PCWP, mmHg	17 ± 6	17 ± 6	18 ± 6	0.5
LVEDP, mmHg	17 ± 6	15 ± 6	17 ± 6	0.3
Cardiac index, L/min/m ²	3.0 ± 0.7	3.0 ± 0.7	3.0 ± 0.7	0.7
Pulmonary vascular resistance, dynes/cm ⁻⁵	222 ± 154	247 ± 185	213 ± 142	0.4
RAP/PCWP ratio	0.48 ± 0.29	0.38 ± 0.18	0.52 ± 0.31	0.08

Variables are depicted as number (percentage), mean ± standard deviation, or median [interquartile range].

LV, left ventricular; LVEDP, left ventricular end-diastolic pressure; PAP, pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; RAP, right atrial pressure; RV, right ventricular; RVEDP, right ventricular end-diastolic pressure; TAPSE, tricuspid annular plane systolic excursion; TR, tricuspid regurgitation.

Associations with increased epicardial adipose tissue and signs of pericardial constraint

Table 2 and Figure 1 demonstrate the echocardiographic and haemodynamic parameters of the entire study population, separated by the absence or presence of a square root sign. Patients with a square root sign had a higher EAT thickness as compared with patients without a square root sign (Table 2 and Figure 1A). BMI and EAT were significantly correlated with each other ($r = 0.71$, $P < 0.001$). Both PCWP and LVEDP were not different between patients with and without a square root sign (Figure 1C,D). However, patients with a square root sign had significantly higher mean RAP as compared with patients without a square root sign (Table 1 and Figure 1E). Although not significant, there was a trend that the RAP/PCWP ratio was also higher in patients with a square root sign (Figure 1F).

Figure 2 depicts an example of a patient with increased EAT thickness alongside the right ventricle (i.e. 6.5 mm), measured with echocardiography, and the presence of a typical square root sign on the RV pressure waveform.

The presence of a square root sign was associated with higher LV septal e' , and there was a trend that the LV lateral/septal e' ratio and RV lateral/LV septal e' ratio were lower in the presence of a square root sign, as seen in Table 2 and Supporting Information, Figure S1.

Associations between epicardial adipose tissue and invasive haemodynamics in men vs. women

Although BMI was more comparable between men and women, EAT thickness was higher in women than in men (Figure 3). While in the entire group, the associations between

Figure 1 (A–F) Association of the square root sign with invasive haemodynamics and epicardial adipose tissue (EAT) thickness. Error bars reflect the standard error of the mean. LVEDP, left ventricular end-diastolic pressure; MRAP, mean right atrial pressure; PCWP, pulmonary capillary wedge pressure; RAP, right atrial pressure; RVEDP, right ventricular end-diastolic pressure.

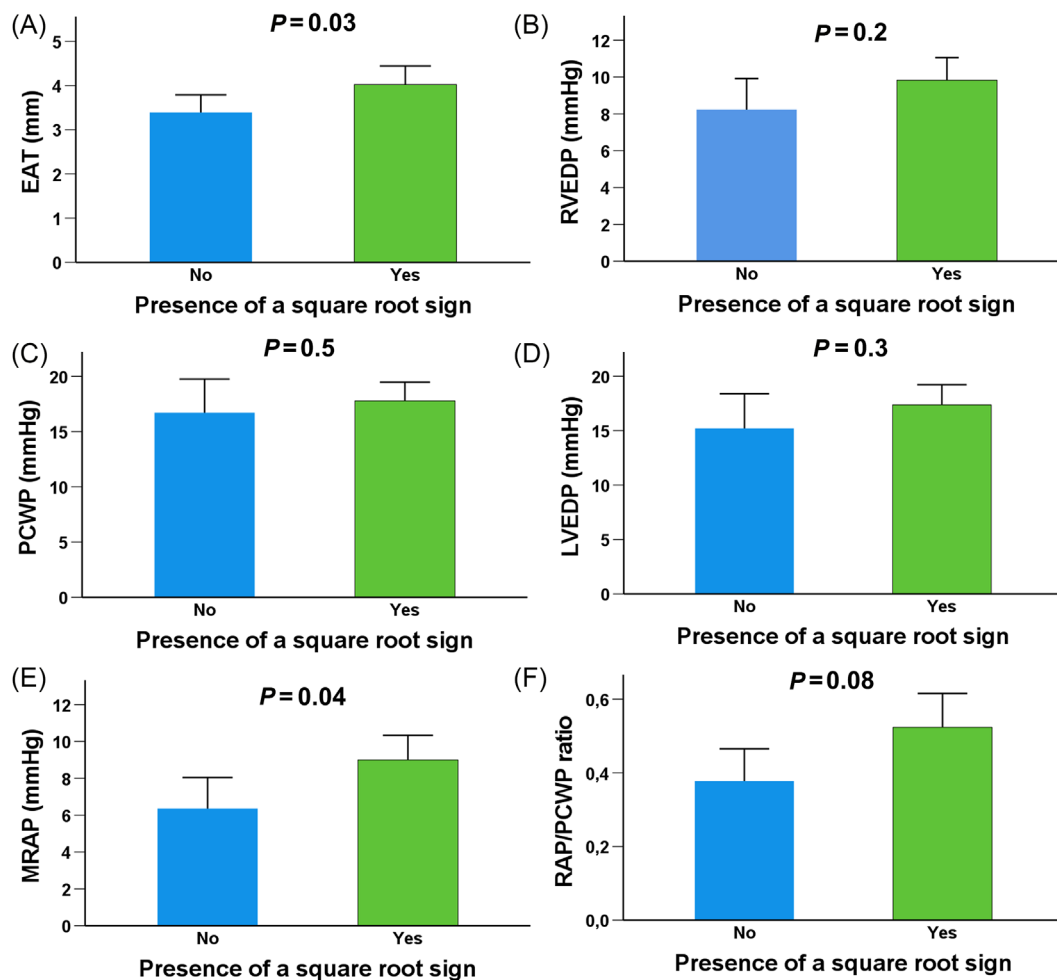


Figure 2 Examples of a patient with and without the presence of a square root sign. The upper panel shows the right heart catheterization registration of a patient with an increased epicardial adipose tissue thickness of 6.5 mm. The right ventricular pressure waveform shows a typical square root sign ('dip and plateau') as shown by the red circles. In this patient, the right ventricular end-diastolic pressure was 11 mmHg, the pulmonary capillary wedge pressure (PCWP) was 13 mmHg, and the mean right atrial pressure (RAP) was 10 mmHg; thus, the RAP/PCWP ratio was 0.77. The lower panel shows a right ventricular pressure waveform without a square root sign. In this patient, the epicardial adipose tissue thickness was 1.9 mm, the right ventricular end-diastolic pressure was 6 mmHg, the PCWP was 9 mmHg, and the mean RAP was 3 mmHg; thus, the RAP/PCWP ratio was 0.33.

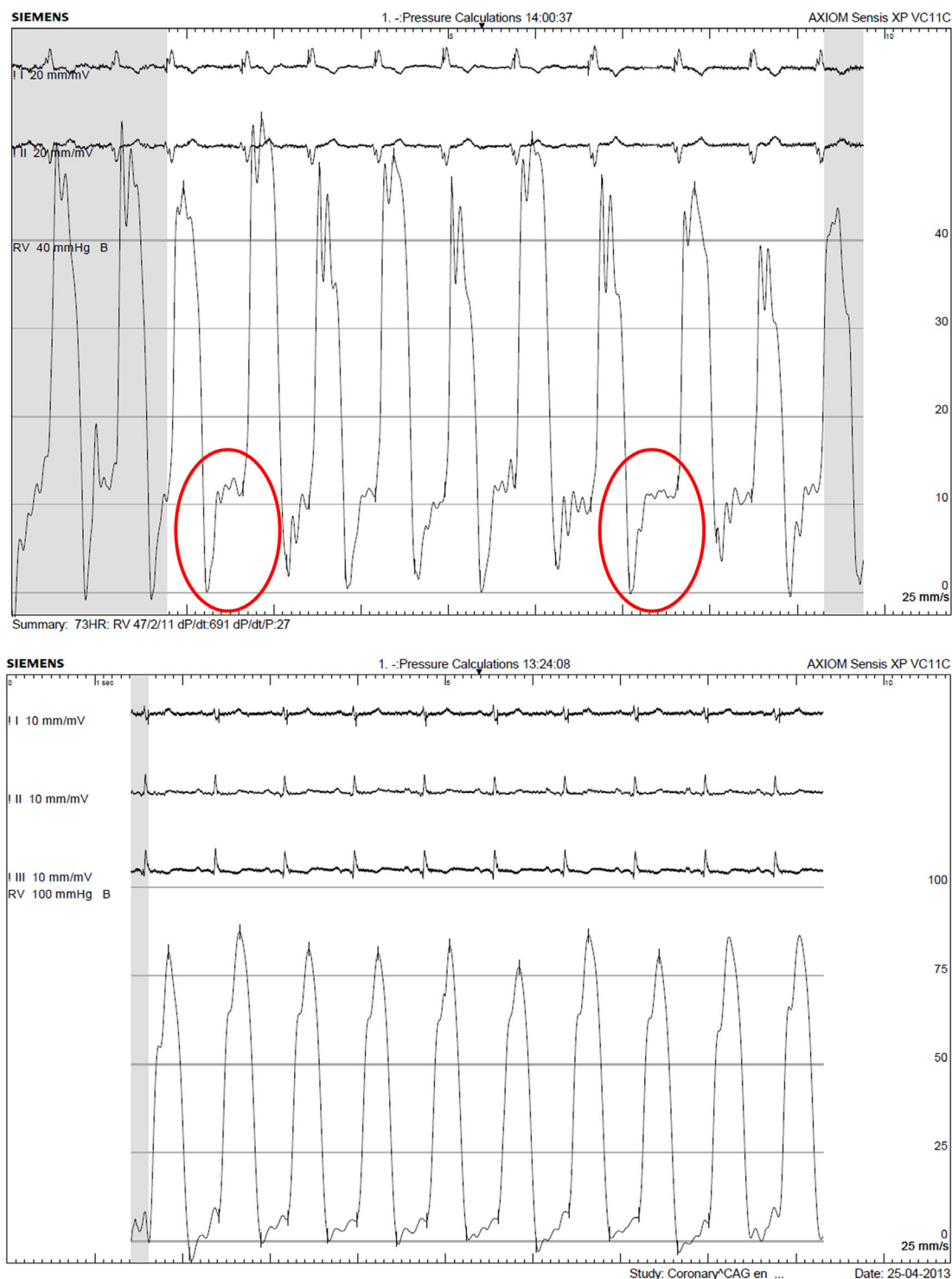


Figure 3 Difference in (A) body mass index (BMI) and (B) epicardial adipose tissue (EAT) between men and women. Error bars reflect the standard error of the mean.

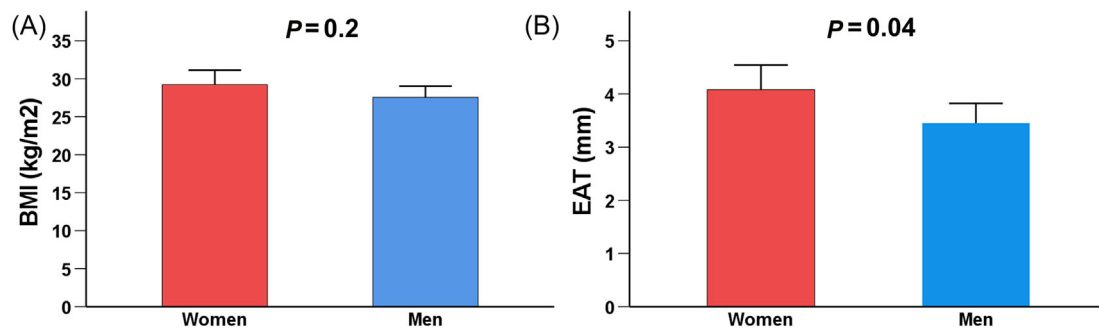
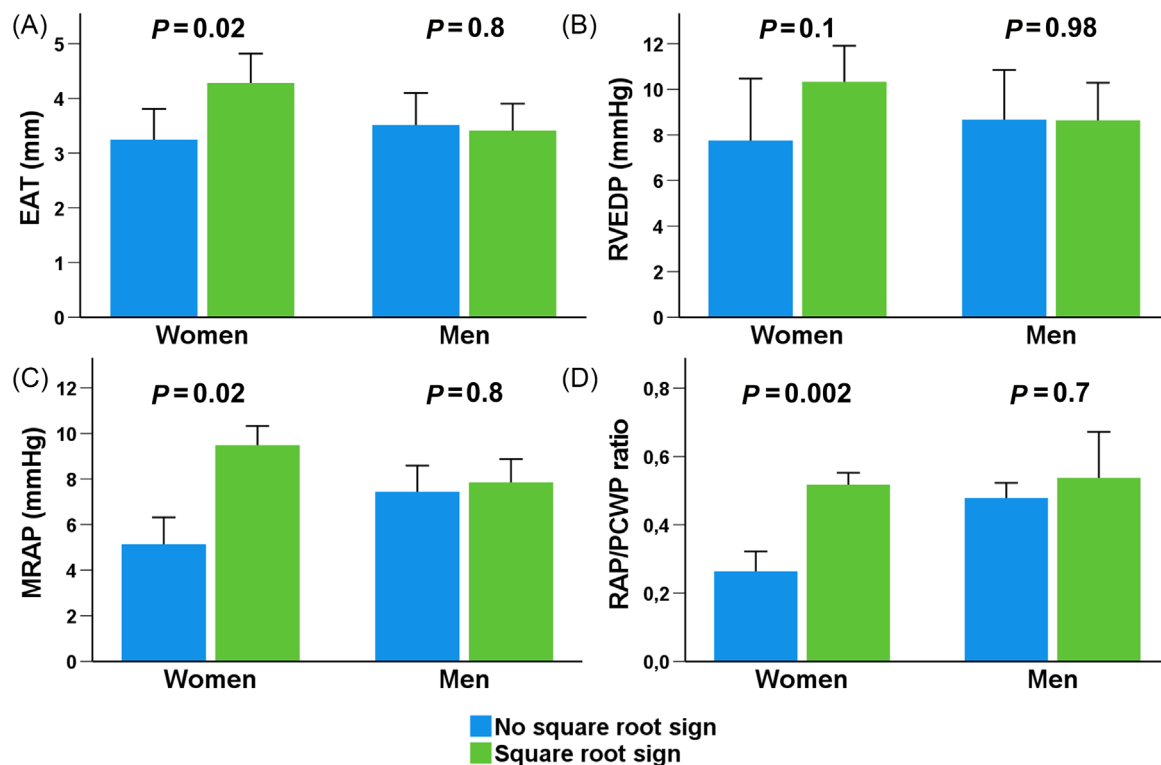


Figure 4 (A–D) Sex-related differences between the association of the square root sign with epicardial adipose tissue (EAT) and invasive haemodynamics. Error bars reflect the standard error of the mean. MRAP, mean right atrial pressure; PCWP, pulmonary capillary wedge pressure; RAP, right atrial pressure; RVEDP, right ventricular end-diastolic pressure.



the presence of a square root sign with EAT thickness and invasive haemodynamics were less pronounced, larger differences were seen when the results were stratified according to sex.

Figure 4A demonstrates that in women, the presence of a square root sign was associated with a higher amount of EAT, whereas this association was not seen in men. Furthermore, the mean RAP and RAP/PCWP ratio were significantly

higher in women who had a square root sign compared with women without a square root sign. On the contrary, such an association was not present in men (Figure 4C,D). However, further interaction analysis showed no significant interaction in the sex-specific associations between the presence of a square root sign and EAT, RVEDP, mean RAP, and RAP/PCWP ratio ($P > 0.05$ for all interaction analyses).

Discussion

The present study showed that the majority of HFpEF patients (i.e. 73%) had a square root sign on the RV pressure waveform. The presence of a square root sign was associated with higher BMI, increased EAT, and elevated right-sided filling pressures. While HFpEF is typically characterized by reduced diastolic tissue velocities, the presence of a square root sign was rather associated with higher diastolic tissue velocities, especially higher septal tissue velocities. Furthermore, the associations between increased EAT and constrictive haemodynamics were mainly seen in women and not in men. These findings suggest that a significant number of obese HFpEF patients with concomitant increased EAT have constrictive haemodynamics. Furthermore, this study may reveal a potential sex-specific difference in the association between obesity, increased EAT, and abnormal invasive haemodynamics in patients with HFpEF.

In the present study, we used the square root sign as an invasive marker for constrictive haemodynamics. While this haemodynamic phenomenon is typically seen in patients with constrictive pericarditis, it is not entirely specific to this disease because it can also be seen in other conditions, mainly in the setting of restrictive cardiomyopathy.¹² Constrictive pericarditis and restrictive cardiomyopathy are two specific types of HF with mostly a preserved LV ejection fraction. Both conditions have a typical clinical and haemodynamic presentation, but the underlying pathophysiology is strikingly different.^{15–17} In restrictive cardiomyopathy, the reduced compliance is mainly caused by abnormal elastic properties of the myocardium itself, whereas in constrictive pericarditis, it is caused by the consequent loss of normal elasticity in the pericardial sac or its content.^{15–17} The latter typically results in impaired ventricular filling in mid and late diastole, and rapid ventricular filling occurs primarily in the early phase of diastole.¹⁸ After the early phase of diastole, the ventricular volume barely increases, which is seen as a square root sign on the RV pressure waveform.¹⁸ In the present study, we examined the haemodynamic features of constrictive pericarditis as a surrogate for the possible constrictive effects that EAT may have on the myocardium in patients with HFpEF. To exclude that the observed associations between increased filling pressures and the presence of a square root sign were due to impaired myocardial relaxation, mimicking restrictive cardiomyopathy, we also assessed myocardial relaxation, and neither the presence of a square root sign nor a higher amount of EAT were associated with impaired myocardial relaxation. On the contrary, the presence of a square root sign was rather associated with *increased* LV septal e' , which is also typically seen in true constrictive pericarditis compared with restrictive cardiomyopathy.¹⁹ This suggests that, in the present study, the presence of a square root sign is more likely the result of reduced compliance of the surrounding

pericardial space—possibly caused by increased EAT thickness—and not the myocardium itself.

While in the entire group, the associations between the amount of EAT and impaired haemodynamics were less pronounced, larger differences were seen when the group was stratified according to sex. Although interaction analyses for potential sex-specific differences were not significant, there was a trend observed that the associations between increased EAT thickness and haemodynamic signs of pericardial constraint were mainly seen in women and not in men with HFpEF. Several pathologic mechanisms might explain the sexual dimorphism in these associations. First, the present findings are in line with the study of Sorimachi *et al.*, where a significant increase in right heart filling pressures was primarily seen in women with HFpEF who had concomitantly excess *abdominal* visceral adipose tissue.²⁰ Although this study did not specifically look at *epicardial* adipose tissue and, in the present study, we did not have measures of abdominal visceral adipose tissue at our disposal, both fat depots appear to be interrelated. The rise in cardiac filling pressures due to excess adipose tissue might be explained by direct mechanical compression, and in women, this phenomenon may be more vigorous than in men. Oestrogen deficiency in post-menopausal women results in a rather rapid shift of fat distribution and subsequently a potential rapid accumulation of EAT, whereas this distribution favours visceral fat.²¹ According to Packer *et al.*, particularly post-menopausal women are forming more proinflammatory mediators such as aldosterone and leptin. Therefore, women are likely hormonally more prone to the formation of epicardial adipocytes.²² Specifically, post-menopausal women with type 2 diabetes mellitus are susceptible to developing EAT depots and exhibit a significantly higher EAT thickness.²³ This may result in the inability of the pericardium to dilate sufficiently, hypothetically leading to pericardial constraint in women, causing increased cardiac filling pressures and reduced exercise capacity.^{24,25} This may be explained by the inability of the heart to dilate sufficiently during exercise in order to keep up with the increased venous return, leading to ventricular interdependence, diminished LV preload, and ultimately reduced cardiac output and exercise intolerance.⁹ Second, the haemodynamic abnormalities seen in the present study may also be explained by enhanced sodium retention and subsequent plasma volume overload in the setting of obesity.⁹ For instance, leptin is secreted by dysfunctional adipose tissue cells, and this has a major impact on the renin-angiotensin system.²⁶ Particularly in women, leptin promotes sodium retention by stimulating the renin-angiotensin system and aldosterone secretion.^{27,28} In the setting of increased plasma volume, constrictive haemodynamics are typically amplified.¹⁸ Still, very little is known about these mechanisms, and they need to be studied more thoroughly in larger cohorts.

The number of patients in which a square root sign was present was relatively high (i.e. 73%), which could be attributed to the preselection of our patient population for a prior sildenafil trial.¹¹ This selection process could have resulted in a relatively higher proportion of patients with increased right-sided pressures. The diastolic plateau serves as a haemodynamic marker for impaired RV diastolic filling, which may be caused by pulmonary hypertension.²⁹ However, we observed no difference in mean PAP or PVR between both groups, while mean RAP was higher in those with a square root sign. This suggests that not increased RV afterload but rather RV filling pressures due to pericardial constraint are the main cause of this finding. A second plausible explanation for this finding is that a substantial proportion of our study population comprises women (64%). Packer *et al.* have previously elucidated that women exhibit significantly greater cardiac filling pressures due to increased ventricular wall stiffness. The more active inflammatory-metabolic phenotype observed in women could serve as another potential explanation for the finding that many patients in the present study had a square root sign observation.²²

Limitations

This study has several limitations. First, the sample size is modest, which limits the ability to adjust for confounding factors. For instance, it could not be further determined to what extent the observed associations between EAT and haemodynamic abnormalities are entirely independent from overall obesity. Therefore, the results must be viewed largely as hypothesis generating. Second, this work was conducted in a tertiary referral centre, causing potential referral bias. Third, echocardiography, instead of cardiac magnetic resonance imaging (MRI), was used to measure EAT. Cardiac MRI provides a more direct, quantitative assessment of the amount of EAT. However, simultaneous assessment of invasive haemodynam-

ics with cardiac magnetic resonance is largely impractical. Fourth, while we used right- and left-sided heart catheterization with simultaneous echocardiography, we did not have simultaneous right and left heart catheterization with respiratory variation at our disposal. For instance, we were not able to calculate the systolic area index at inspiration and expiration, which is considered a more sensitive marker for the assessment of constrictive pericarditis. However, surrogate measures such as a square root sign and RAP/PCWP ratio were used in combination with tissue Doppler imaging, underscoring a constrictive pericarditis-like phenomenon instead of a restrictive cardiomyopathy-like phenomenon.

Conclusions

Obesity and concomitant epicardial adiposity are associated with haemodynamic signs of pericardial constraint in patients with HFpEF. This phenomenon was particularly present in women and not in men. The pathophysiological and therapeutic implications of increased EAT in patients with HFpEF need further investigation.

Conflict of interest

None declared.

Supporting information

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

Figure S1. Association between the square root sign and tissue Doppler velocities.

References

1. Van Woerden G, van Veldhuisen DJ, Westenbrink BD, de Boer RA, Rienstra M, Gorter TM. Connecting epicardial adipose tissue and heart failure with preserved ejection fraction: Mechanisms, management and modern perspectives. *Eur J Heart Fail* 2022;**24**:2238-2250. doi:10.1002/ehf.2741
2. Packer M. Drugs that ameliorate epicardial adipose tissue inflammation may have discordant effects in heart failure with a preserved ejection fraction as compared with a reduced ejection fraction. *J Card Fail* 2019;**25**:986-1003. doi:10.1016/j.cardfail.2019.09.002
3. Mahabadi AA, Anapliotis V, Dykun I, Hendricks S, Al-Rashid F, Lüdtke P, *et al.* Epicardial fat and incident heart failure with preserved ejection fraction in patients with coronary artery disease. *Int J Cardiol* 2022;**357**:140-145. doi:10.1016/j.ijcard.2022.04.009
4. Kenchaiah S, Ding J, Carr JJ, Allison MA, Budoff MJ, Tracy RP, *et al.* Pericardial fat and the risk of heart failure. *J Am Coll Cardiol* 2021;**77**:2638-2652. doi:10.1016/j.jacc.2021.04.003
5. Koepp KE, Obokata M, Reddy YNV, Olson TP, Borlaug BA. Hemodynamic and functional impact of epicardial adipose tissue in heart failure with preserved ejection fraction. *JACC Heart Fail* 2020;**8**:657-666. doi:10.1016/j.jchf.2020.04.016
6. 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. doi:10.1002/ejhf.1283
7. Van Woerden G, van Veldhuisen DJ, Manintveld OC, van Empel VPM, Willems TP, de Boer RA, *et al.* Epicardial adipose tissue and outcome in heart failure with mid-range and preserved ejection fraction. *Circ Heart Fail* 2022;**15**:e009238. doi:10.1161/CIRCHEARTFAILURE.121.009238
 8. Gorter TM, van Woerden G, Rienstra M, Dickinson MG, Hummel YM, Voors AA, *et al.* Epicardial adipose tissue and invasive hemodynamics in heart failure with preserved ejection fraction. *JACC Heart Fail* 2020;**8**:667-676. doi:10.1016/j.jchf.2020.06.003
 9. Obokata M, Reddy YNV, Pislaru SV, Melenovsky V, Borlaug BA. Evidence supporting the existence of a distinct obese phenotype of heart failure with preserved ejection fraction. *Circulation* 2017;**136**:6-19. doi:10.1161/CIRCULATIONAHA.116.026807
 10. Gorter TM, van Veldhuisen DJ, Voors AA, Hummel YM, Lam CSP, Berger RMF, *et al.* Right ventricular-vascular coupling in heart failure with preserved ejection fraction and pre- vs. post-capillary pulmonary hypertension. *Eur Heart J Cardiovasc Imaging* 2018;**19**: 425-432. doi:10.1093/ehjci/jex133
 11. Hoendermis ES, Liu LC, Hummel YM, van der Meer P, de Boer RA, Berger RM, *et al.* Effects of sildenafil on invasive haemodynamics and exercise capacity in heart failure patients with preserved ejection fraction and pulmonary hypertension: A randomized controlled trial. *Eur Heart J* 2015;**36**:2565-2573. doi:10.1093/eurheartj/ehv336
 12. Welch TD. Constrictive pericarditis: Diagnosis, management and clinical outcomes. *Heart* 2018;**104**:725-731. doi:10.1136/heartjnl-2017-311683
 13. Van Woerden G, van Veldhuisen DJ, Gorter TM, Ophuis B, Saucedo-Orozco H, van Empel VPM, *et al.* The value of echocardiographic measurement of epicardial adipose tissue in heart failure patients. *ESC Heart Fail* 2022;**9**:953-957. doi:10.1002/ehf2.13828
 14. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, *et al.* Recommendations for cardiac chamber quantification by echocardiography in adults: An update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging* 2015;**16**:233-270. doi:10.1093/ehjci/jev014
 15. Yang ZY, Wang H, Chang SS, Cui J, Zhou L, Lv Q, *et al.* Left ventricular strain-curve morphology to distinguish between constrictive pericarditis and restrictive cardiomyopathy. *ESC Heart Fail* 2022;**8**:4863-4872. doi:10.1002/ehf2.13679
 16. Garcia MJ. Constrictive pericarditis versus restrictive cardiomyopathy? *J Am Coll Cardiol* 2016;**67**:2061-2076.
 17. Hatle LK, Appleton CP, Popp RL. Differentiation of constrictive pericarditis and restrictive cardiomyopathy by Doppler echocardiography. *Circulation* 1989;**79**:357-370. doi:10.1161/01.CIR.79.2.357
 18. Geske JB, Anavekar NS, Nishimura RA, Oh JK, Gersh BJ. Differentiation of constriction and restriction: Complex cardiovascular hemodynamics. *J Am Coll Cardiol* 2016;**68**:2329-2347. doi:10.1016/j.jacc.2016.08.050
 19. Choi JH, Choi JO, Ryu DR, Lee SC, Park SW, Choe YH, *et al.* Mitral and tricuspid annular velocities in constrictive pericarditis and restrictive cardiomyopathy: Correlation with pericardial thickness on computed tomography. *JACC Cardiovasc Imaging* 2011;**4**:567-575. doi:10.1016/j.jcmg.2011.01.018
 20. Sorimachi H, Obokata M, Takahashi N, Reddy YNV, Jain CC, Verbrugge FH, *et al.* Pathophysiologic importance of visceral adipose tissue in women with heart failure and preserved ejection fraction. *Eur Heart J* 2021;**42**: 1595-1605. doi:10.1093/eurheartj/ehaa823
 21. Kim SA, Kim MN, Shim WJ, Park SM. Epicardial adipose tissue is related to cardiac function in elderly women, but not in men. *Nutr Metab Cardiovasc Dis* 2017;**27**:41-47. doi:10.1016/j.numecd.2016.11.001
 22. Packer M, Lam CSP, Lund LH, Maurer MS, Borlaug BA. Characterization of the inflammatory-metabolic phenotype of heart failure with a preserved ejection fraction: A hypothesis to explain influence of sex on the evolution and potential treatment of the disease. *Eur J Heart Fail* 2020;**22**:1551-1567. doi:10.1002/ejhf.1902
 23. Wu FZ, Huang YL, Wang YC, Lin HS, Chen CS, Ju YJ, *et al.* Impact of location of epicardial adipose tissue, measured by coronary artery calcium-scoring computed tomography on obstructive coronary artery disease. *Am J Cardiol* 2013;**112**:943-949. doi:10.1016/j.amjcard.2013.05.022
 24. Mehta A, Mehta M, Jain AC. Constrictive pericarditis. *Clin Cardiol* 1999;**22**: 334-344. doi:10.1002/clc.4960220509
 25. Wu CK, Tsai HY, Su MM, Wu YF, Hwang JJ, Lin JL, *et al.* Evolutional change in epicardial fat and its correlation with myocardial diffuse fibrosis in heart failure patients. *J Clin Lipidol* 2017;**11**: 1421-1431. doi:10.1016/j.jacl.2017.08.018
 26. Packer M. Derangements in adrenergic-adipokine signalling establish a neuro-hormonal basis for obesity-related heart failure with a preserved ejection fraction. *Eur J Heart Fail* 2018;**20**:873-878. doi:10.1002/ejhf.1167
 27. Xue B, Yu Y, Zhang Z, Guo F, Beltz TG, Thunhorst RL, *et al.* Leptin mediates high-fat diet sensitization of angiotensin II-elicited hypertension by upregulating the brain renin-angiotensin system and inflammation. *Hypertension* 2016;**67**: 970-976. doi:10.1161/HYPERTENSIONAHA.115.06736
 28. Huby AC, Antonova G, Groenendyk J, Gomez-Sanchez CE, Bollag WB, Filosa JA, *et al.* Adipocyte-derived hormone leptin is a direct regulator of aldosterone secretion, which promotes endothelial dysfunction and cardiac fibrosis. *Circulation* 2015;**132**:2134-2145. doi:10.1161/CIRCULATIONAHA.115.018226
 29. Grupper A, Kodesh A, Lavee J, Fefer P, Barbash IM, Elian D, *et al.* Diastolic plateau—Invasive hemodynamic marker of adverse outcome among left ventricular assist device patients. *Front Cardiovasc Med* 2022;**9**:847205. doi:10.3389/fcvm.2022.847205