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Pathophysiologic Consequences of Pericardial Adipose Tissue Assessed by Magnetic Resonance Imaging

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by

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Abstract

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The University of Texas at Arlington, 2024

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Obesity is a major contributor to cardiovascular disease; however, the exact mechanism remains incompletely understood. Conventional metrics, like body mass index, fail to represent fat distribution and its impact on health. A growing body of literature suggest differences between subcutaneous and visceral fat in relation to cardiovascular risk. This specificity has also been extended to the fat surrounding the heart, collectively known as pericardial fat, which includes epicardial adipose tissue (EAT)— located between the myocardium and the visceral layer of the pericardium— and paracardial adipose tissue (PAT)—found outside the parietal pericardium in the mediastinum. Importantly, these two depots have distinct characteristics, potentially contributing to heart disease in different ways.

This dissertation uses advanced imaging, specifically magnetic resonance imaging (MRI), to evaluate the pathophysiologic consequences of excess pericardial fat. Specifically, in Chapter 2, we evaluate the role of epicardial Fat on coronary vascular function, cardiac morphology and cardiac function in a cohort of women with signs and symptoms of ischemia but no obstructive coronary artery disease – all of whom underwent invasive coronary angiography with coronary

function testing. In Chapter 3, we evaluate whether excess adipose tissue can be mechanically constraining and contribute to adverse cardio-mechanical interaction in heart failure with preserved ejection fraction. Chapter 4 provides a detailed literature review, including findings from Chapters 2 and 3. Finally, Chapter 5 summarizes the major findings and offers a brief interpretation of results and future directions.

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Acknowledgments

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Chapter 1

Introduction

Obesity is a significant factor in the development of cardiovascular disease, yet the exact mechanisms remain incompletely understood. Conventional measures such as body mass index do not adequately reflect fat distribution or its health implications. Research increasingly indicates that subcutaneous and visceral fat differ in their relationship to cardiovascular risk.[1] This distinction extends to the fat around the heart, known as pericardial fat, which includes epicardial adipose tissue (EAT)—situated between the myocardium and the visceral pericardium—and paracardial adipose tissue (PAT)—located outside the parietal pericardium in the mediastinum. These two fat depots have unique characteristics and may contribute to heart disease in different ways.

In the early stages, cardiology largely regarded EAT as a passive, inert tissue with primarily mechanical functions, serving as a cushioning layer around the heart. Its significance was predominantly anatomical, providing protection and insulation to the myocardium.[2] Subsequent studies revealed that EAT is not merely a bystander but actively contributes to the pathogenesis of cardiovascular health.[3, 4] EAT tends to increase in volume and thickness as body weight and body mass index increase.[5-7] The presence of excessive EAT was noted in individuals with metabolic syndrome,[8-10] promoting investigations into its metabolic activity and endocrine function. The ability of EAT to secrete bioactive molecules, such as adipokines, cytokines, and inflammatory mediators, emerged as a key mechanism linking EAT to insulin resistance,[9-11] systemic inflammation,[12, 13] dyslipidemia,[14] and hypertension,[15, 16] core components of metabolic syndrome. By impairing insulin signaling pathways, inhibiting lipoprotein lipase activity, and inducing endothelial dysfunction, EAT contributes to a pro-inflammatory microenvironment and

dysregulated lipid metabolism.[17] This cascade of events not only underlies the pathogenesis of metabolic syndrome but also sets the stage for the development of cardiovascular diseases.

EAT, plays significant roles in cardiovascular health, particularly in the context of atherosclerosis and obstructive coronary artery disease (CAD).[18, 19] In terms of atherosclerosis, EAT is metabolically active that contributes directly through paracrine effects. It secretes pro-inflammatory adipokines such as interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-alpha), and leptin, which promote inflammation and endothelial dysfunction in coronary arteries.[4, 14] These processes can initiate and perpetuate the development of atherosclerotic plaques by enhancing vascular inflammation, impairing nitric oxide bioavailability, and promoting the migration and proliferation of vascular smooth muscle cells, ultimately contributing to the pathophysiology of CAD.[20] Moreover, anatomical proximity of EAT to coronary arteries allows for direct mechanical compression, potentially compromising coronary blood flow and increasing the risk of myocardial ischemia and angina.[21] Clinical studies have demonstrated associations between increased EAT volume and the severity of obstructive CAD. Higher EAT thickness correlates with the presence and extent of coronary artery calcification, a marker of advanced atherosclerosis. Therefore, coronary vascular function in obstructive CAD is compromised.[22, 23] Cardiac morphology and function in patients with obstructive CAD are characterized by significant alterations due to the presence of atherosclerotic plaques that lead to substantial narrowing or blockage of coronary arteries. These structural changes can result in reduced myocardial perfusion, particularly during periods of increased oxygen demand, which in turn can precipitate ischemic episodes.[24] Over time, chronic ischemia and intermittent episodes of myocardial infarction contribute to the remodeling of the heart muscle, including hypertrophy

and fibrosis, which compromise cardiac function. This remodeling often manifests as left ventricular hypertrophy and dilation, ultimately leading to reduced systolic and diastolic function.[25, 26] Furthermore, obstructive CAD is frequently associated with decreased ejection fraction, impaired contractility, and an increased risk of heart failure.[27]

Currently, the understanding of EAT's contribution to coronary vascular function remains less clear compared to its role in obstructive CAD. While EAT's secretion of adipokines and cytokines likely contributes to local inflammation and endothelial dysfunction, the extent to which these factors contribute to coronary vascular function remains uncertain. Further research is therefore needed to elucidate whether EAT plays a significant role in initiating coronary vascular dysfunction. Moreover, the role of EAT on cardiac morphology and function remain unclear. Chapter 2 addresses this question by examining epicardial fat, coronary vascular function, and cardiac morphology and function in women with suspected INOCA through invasive coronary function testing and cardiac MRI.

Studies also show that excessive pericardial fat can impose physical constraints that influence cardiac function through a phenomenon called ventricular interdependence. This process involves mechanical interactions between the right and left ventricles, primarily driven by elevated pressures within the right ventricle and the limited space within the pericardium.[7] As pericardial fat accumulates, it occupies the space around the heart, potentially restricting the expansion and contraction of both ventricles during the cardiac cycle. In conditions where right-sided pressures increase dynamically, such as in pulmonary hypertension or severe lung diseases, the presence of significant EAT can exacerbate ventricular interdependence. This can lead to

compromised filling of the left ventricle due to the reduced capacity of the right ventricle to expand fully within the confined pericardial space. As a result, cardiac output may be impaired, contributing to symptoms such as dyspnea (shortness of breath) and exercise intolerance.[28] Evidence for this, however, remains limited to observations using transthoracic echocardiography under resting conditions. Given that exercise can potentially worsen cardio-mechanical interaction by enhancing venous return through skeletal muscle and respiratory pumps, additional investigation is justified. Therefore, Chapter 3 addresses this gap by investigating the relationship between excess pericardial fat and adverse cardio-mechanical interaction in heart failure with preserved ejection fraction, both at rest and during exercise, utilizing cardiac MRI.

Together, the results from this dissertation will expand our understanding of the roles that EAT and PAT play in cardiac function and disease. By elucidating the contributions of EAT to coronary vascular function, as well as cardiac morphology and function in women with suspected INOCA and investigating the impact of EAT and PAT on cardio-mechanical interactions in HFpEF patients, these studies will provide valuable insights into the mechanisms underlying cardiovascular diseases.

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Kitzman D. Exercise Intolerance in Older Adults With Heart Failure With Preserved Ejection Fraction: JACC State-of-the-Art Review. *J Am Coll Cardiol*. 2021;78:1166-1187.

Chapter 2

Impact of Epicardial Fat on Coronary Vascular Function, Cardiac Morphology, and Cardiac Function in Women with Suspected INOCA

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Abstract

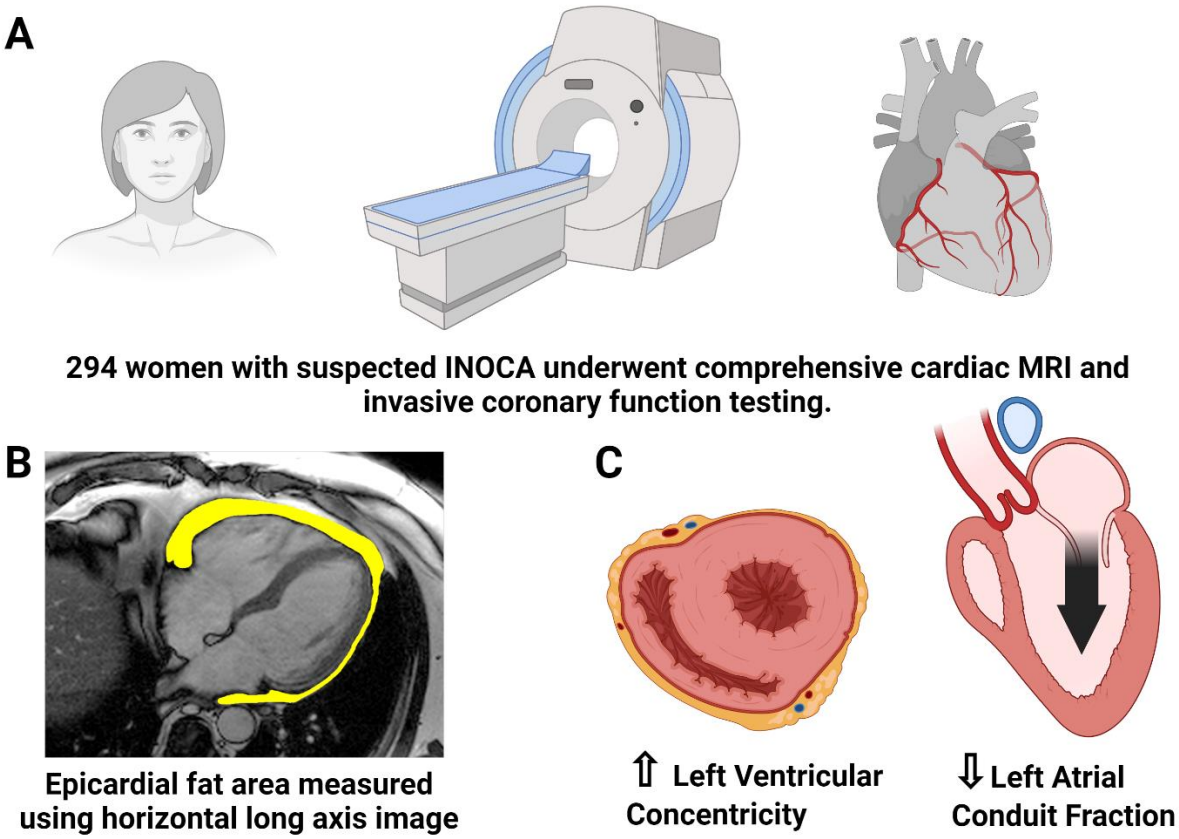
Introduction: Epicardial fat is a metabolically active adipose tissue depot situated between the myocardium and visceral pericardium that covers ~80% of the heart surface. While epicardial fat has been associated with the development of atherosclerotic coronary artery disease (CAD), less is known about the relationship between epicardial fat and coronary vascular function. Moreover, the relations between excess epicardial fat and cardiac morphology and function remains incompletely understood.

Methods and Results: To address these knowledge gaps, we retrospectively analyzed data from 294 individuals from our database of women with suspected ischemia with no obstructive coronary disease (INOCA) who underwent both invasive coronary function testing and cardiac magnetic resonance imaging (cMRI). Epicardial fat area, biventricular morphology, and function, as well as left atrial function, were assessed from cine images, per established protocols. The major novel findings were twofold: First, epicardial fat area was not associated with coronary vascular dysfunction. Second, epicardial fat was associated with increased left ventricular concentricity (β= 0.15, p= 0.01), increased septal thickness (β= 0.17, p= 0.002), and reduced left atrial conduit fraction (β= -0.15, p= 0.02), even after accounting for age, BMI, and history of hypertension.

Conclusions

Taken together, these data do not support a measurable relationship between epicardial fat and coronary vascular dysfunction but does suggest that epicardial fat may be related to concentric

remodeling and diastolic dysfunction in women with suspected INOCA. Prospective studies are needed to elucidate the long-term impact of epicardial fat in this patient population.



Graphical Abstract: Illustration summarizing the experimental approach and main results, showing that greater epicardial fat area is correlated with increased left ventricular concentricity and reduced left atrial conduit fraction

Introduction

Ischemia with no obstructive coronary artery disease (INOCA) is prevalent in women and is associated with an increased risk of major adverse cardiovascular events, including heart failure with preserved ejection fraction (HFpEF).[1, 2] However, the mechanism(s) contributing to the progression to heart failure remains to be elucidated. One common trait consistently observed in both populations is left ventricular diastolic dysfunction, characterized by impaired early diastolic relaxation, and elevated end-diastolic pressures.[3-6] Identifying mechanism(s) contributing to diastolic dysfunction in INOCA is therefore critically important for understanding disease progression and developing new therapeutic interventions.

Epicardial fat— a metabolically active adipose tissue covering approximately 80% of the heart surface— secretes bioactive molecules that adversely modulate vascular inflammation. This has indeed been associated with the development of coronary atherosclerosis and cardiovascular disease.[7-9] Epicardial fat has also been implicated in the development of adverse ventricular remodeling and left ventricular diastolic dysfunction, including in those with aortic stenosis,[10] atrial fibrillation,[11] and non-ischemic cardiomyopathy.[12] The extent to which excess epicardial fat contributes to coronary vascular dysfunction remains largely unexplored. Moreover, the extent to which excess epicardial fat contributes to adverse ventricular remodeling and cardiac dysfunction in women with INOCA remain unclear. We hypothesized that epicardial fat content would be directly related to worse coronary vascular function, adverse left ventricular remodeling, and diastolic dysfunction.

Methods

Study population

To address our specific research question, data were leveraged from the Women's Ischemia Syndrome Evaluation (WISE) database, which includes participants undergoing invasive measurement of left ventricular end-diastolic pressure, coronary reactivity testing, and comprehensive cardiac magnetic resonance imaging (NCT03876223, NCT02582021, NCT00832702). Prior to participating in any research protocols, all participants provided written informed consent.

Common exclusion criteria for participants included the following: the presence of obstructive coronary artery disease (≥50% stenosis), occurrence of acute coronary syndrome within the last three months, chest pain attributed to a non-ischemic etiology, necessity for valve repair or replacement, patients experiencing cardiogenic shock, left ventricular ejection fraction <50%, history of previous percutaneous coronary intervention or coronary artery bypass grafting, presence of end-stage renal or liver disease, life expectancy <4 years, or inability to provide informed consent. Due to limited male enrollment to-date (<5 total), only female participants were included herein.

Coronary Function Testing and Left Ventricular Filling Pressure

Participants fasted overnight and refrained from consuming caffeine, long-acting nitrates, and other vasoactive agents for at least 24 hours before testing. On the testing day, participants were instructed to abstain from nicotine and avoid sublingual nitroglycerin for at least four hours prior to the procedure.

Coronary angiography was performed to rule out previously undiagnosed obstructive

epicardial coronary artery disease, or other abnormalities. Subsequently, resting left ventricular end-diastolic pressure (LVEDP) was assessed using a pig-tail catheter before any provocative testing.

To evaluate coronary vascular reactivity, a Doppler wire (Flowire, Volcano Inc) was inserted into the proximal left anterior descending artery (LAD). Coronary micro- and macrovascular dilation and constriction pathways were tested by infusing intra-coronary adenosine (18 mcg, 18 mcg, and 36 mcg), acetylcholine (0.182 mcg/mL and 18.2 mcg/mL), and nitroglycerin (200 mcg) directly into the LAD, as previously described.[6] Coronary blood flow velocity (CBF) and coronary cine angiography were obtained after each infusion. All data were analyzed by a core laboratory, with analysis blinded to all clinical data.

Epicardial Fat Area, Cardiac Morphology, and Cardiac Function

On a separate visit, cardiac magnetic resonance imaging (CMRI) was conducted while in a supine position, utilizing either a 1.5-Tesla (Avanto) or 3-Tesla (Vida) Siemens scanner (Siemens Healthineers, Erlangen, Germany). Images were ECG gated and acquired with a phased-array surface coil. Assessment of epicardial fat area, cardiac morphology, and cardiac function was performed using a series of steady-state free precession cine images. These images were prescribed perpendicular to the long-axis of the ventricles (i.e., short-axis view), covering the apex to the base, along with long-axis images in the horizontal and vertical imaging planes (slice thickness: 8 mm, with 25 cardiac phases).[13] The analysis of data was conducted by a single observer (S.K.Z) who was blinded to each participant's medical history. Commercially available software (CVI[42]; V 5.13.5, Circle Cardiovascular Imaging Inc., Calgary, AB, Canada) was used for all analysis.

The measurement of epicardial fat area was derived from a single high-resolution steady-state free precession cine image in the horizontal long-axis imaging plane; validated by our group against three-dimensional cardiac computed tomography (see ***Supplemental Material*** for details). All data were analyzed by the same reader (S.K.Z), in whom inter-rater reproducibility, expressed as a coefficient of variation, was 3.7%.

To assess right and left ventricular volumes, the endocardial border of each short-axis slice was manually traced at end-diastole and end-systole, with volumes derived using the method of disks. Stroke volume and ejection fraction were calculated based on these measurements. Left ventricular mass was determined by including epicardial border contours at end-diastole. Both mass and volume were expressed as absolute values and indexed to body surface area. Left ventricular concentricity was calculated by dividing mass by end-diastolic volume.

Left and right ventricular strain/strain rate were measured by feature tracking, a method previously performed[14] and validated[15-17] by our group. Specifically, for left ventricular strain/strain rate, the endo- and epicardial borders of the short and long-axis cine images were manually delineated at end-diastole and end-systole before applying the feature tracking algorithm. Care was taken to exclude short axis slices containing the left ventricular outflow tract and/or left atrium, apical slices lacking clear delineation of the ventricular lumen at end-systole (at least 2cm proximal to luminal obliteration), and slices with insufficient tracking quality. For right ventricular strain measurements, only the longitudinal strain/strain rate was measured, using the horizontal long-axis view, as the anatomy and function of the right ventricle may not lend itself towards reliable radial and circumferential strain.[18]

Left atrial (LA) volume was determined using the biplane area-length method.[19] To assess left atrial strain/strain rate, the endo- and epicardial boarders of the atrium were manually traced at end-diastole and end-systole in the horizontal and vertical long-axis cine images, as described previously by our group.[20] Left atrial function was characterized by three distinct phases: reservoir, when the left atrium passively receives blood from the pulmonary circulation; conduit, when blood flows passively from the atrium to the ventricle along the transmitral pressure gradient; and booster, when the left atrium contracts, transferring blood into the ventricle.

Statistical methods

The data analyses utilized IBM SPSS Statistics 29, and all results are presented as mean ± standard deviation unless otherwise specified. To examine the impact of epicardial fat on outcome measures, participants were categorized into tertiles based on epicardial fat area.

Group comparisons were conducted using Kruskal-Wallis tests to compare the three groups on the outcome measures. This non-parametric test was selected as an alternative to the one-way ANOVA due to its robustness against non-normal distributions and variance heterogeneity. For nominal variables, the Pearson chi-square test was employed, with Dunn's post-hoc analysis to further investigate significant differences among groups.

Multiple linear regression analyses were conducted to assess the relationship between epicardial fat and the outcome measures. Subsequently, adjustments were made for covariates (age, BMI, and history of hypertension) to determine whether any observed relationships persisted or changed after considering these additional factors. Collinearity diagnostics were employed to evaluate the degree of multicollinearity among the independent variables.

Additionally, the heteroscedasticity assumption was assessed to ensure that the variability of the residuals remained consistent across all levels of the independent variables. Beta coefficients (β) were subsequently reported to quantify the strength and direction of the relationship between epicardial fat and the outcome measures.

Throughout all tests, two-sided p-values of ≤0.05 were considered indicative of statistical significance.

Results

Participant characteristics are summarized in **Table 1**, grouped according to epicardial fat area (in tertiles). The high epicardial fat group was older and had a higher body mass index (BMI) and body surface area (BSA). Additionally, this group displayed higher mean arterial pressure, elevated LVEDP, a greater history of hypertension, and scored higher in total coronary severity.

As outlined in **Table 2**, the high epicardial fat group also exhibited lower bi-ventricular end-diastolic volume and stroke volume, greater left ventricular concentricity, and septal wall thickness, reduced left atrial ejection fraction and conduit fraction, along with reduced bi-ventricular early diastolic strain rates, and lower left atrial reservoir and conduit strain rates.

As outlined in **Table 3**, multiple linear regression was performed with age, BMI, history of hypertension, and epicardial fat as the predictors of the outcome variables. Notably, elevated epicardial fat were found to significantly predict increased left ventricular concentricity (β= 0.15, p= 0.01) and septal thickness (β= 0.17, p= 0.002). Conversely, there was a significant inverse relationship observed between epicardial fat and left atrial conduit fraction, indicating that elevated epicardial fat significantly predicted lower conduit fraction (β= -0.15, p= 0.02).

Discussion

In this well-phenotyped cohort of women with suspected INOCA, we report two novel findings: First, epicardial fat is not associated with coronary vascular dysfunction, as measured by core laboratory adjudicated invasive coronary angiography. Second, while epicardial fat is associated with changes in bi-ventricular morphology and diastolic dysfunction in unadjusted models, only left ventricular concentricity, septal thickness, and left atrial conduit fraction were independently associated following adjustment for age, BMI, and history of hypertension.

Several studies have reported direct associations between epicardial fat and obstructive coronary artery disease.[21-24] Indeed, epicardial fat secretes profibrotic and proinflammatory factors which are believed to drive the development of atherosclerosis.[25] We too observed stepwise differences in the coronary severity score, being highest in those with the greatest epicardial fat. However, less is known regarding the association between epicardial fat and coronary vascular function. In patients with suspected CAD and normal myocardial perfusion, epicardial fat (measured by computed tomography) was predictive of myocardial hyperemia and reduced myocardial perfusion reserve (measured by ^{82}Rb positron emission tomography). However, Nakanishi et al. found no correlation between multi-detector computed tomography-derived epicardial fat volume and transthoracic doppler echocardiography-derived coronary flow reserve.[26] To the best of our knowledge, however, this is the first study to evaluate the association between epicardial fat and coronary vascular function with direct coronary function testing. In contrast to our hypothesis, however, epicardial fat was not associated with macrovascular nor microvascular coronary dysfunction. We interpret these findings to suggest that coronary vascular dysfunction is a complex process, influenced by many factors beyond local

paracrine secretion from epicardial adipose tissue. For example, the participants in this investigation were, on average, 10-15 years younger with no or non-obstructive coronary arteries compared to those described in prior studies with obstructive coronary artery disease.[8, 22, 24] Moreover, all the participants in this investigation were women, where the overwhelming majority of participants in prior studies were men.[27-29] Thus, it remains unknown if the association between epicardial fat and coronary vascular dysfunction is sexually dimorphic, or if it will change following chronic exposure over the next 5-15 years. This is indeed an important area of future investigation.

While epicardial fat was associated with adverse cardiac morphology and diastolic dysfunction, only left ventricular concentricity, septal thickness, and left atrial conduit fraction were independently associated with excess epicardial fat. This is consistent with previous observations showing that epicardial fat and visceral fat have comparable associations with cardiovascular risk factors and the metabolic syndrome.[30, 31] Moreover, in a recent study which included >44,000 participants from the UK biobank, the association between epicardial and pericardial adiposity and incident cardiovascular disease was largely explained by abdominal visceral adiposity.[32] In a separate analysis of the UK biobank, the investigators further show that epicardial and pericardial adiposity was linked with an unhealthy left ventricular structure (greater wall thickness, higher left ventricular mass, more concentric pattern of left ventricular remodeling) and poorer left ventricular function. However, these differences were largely mediated by hypertension.[30] Thus, the data herein both confirm and extend prior reports, suggesting that elevated epicardial fat is an important prognostic indicator of unhealthy cardiac structure and function (i.e., enhanced concentricity), while further suggesting it may be an

independent contributor to diastolic dysfunction.

While the exact mechanism linking epicardial fat with adverse concentric remodeling and diastolic dysfunction remains unknown, several factors may be contributing. For example, women are more likely to develop concentric patterns of LV remodeling than men, together with diastolic dysfunction. Moreover, epicardial fat shares a blood supply with the myocardium, and is metabolically active, serving as a source of both adipokines and metabolic substrate. Inflammation is indeed recognized for its role in promoting diffuse fibrosis and altering the extracellular matrix. Moreover, fatty acids (especially palmitic acid, myristic acid and palmitoleic acid) have been shown to promote the abnormal production of myocardial growth factors associated with mammalian target of rapamycin (mTOR) phosphorylation. We therefore expect that a combination of these, and other factors not yet identified, likely contributed to the present findings. Future studies are therefore warranted to define specific mechanisms and identify putative treatment targets.

Strengths and Limitations

The strengths of this investigation include well phenotyped women with suspected INOCA undergoing gold-standard coronary vascular function testing and cardiac MRI. Moreover, that epicardial fat was measured from routinely acquired MRI images makes the approach highly translatable. Also, that we extend our observations beyond the left ventricle to include functional analysis of the left atrium and right ventricle extends prior reports in the area.

A limitation of this study is that all the participants included had signs and symptoms of ischemia warranting clinical coronary vascular function testing. However, as reported in the results, not all the women studied had impaired coronary vascular function, providing an adequate range to test

whether epicardial fat is associated with coronary vascular dysfunction. A further limitation is the focus on only female participants. However, this is also a strength, as the population studied herein have an increased risk of developing heart failure with preserved ejection fraction with no clear mechanism yet established. Thus, this investigation adds to a growing body of literature in this specific research area.

Conclusions

Taken together, these data do not support a relationship between epicardial fat and coronary vascular dysfunction but does suggest that epicardial fat may play an important role in the development of concentric remodeling and diastolic dysfunction in women with suspected INOCA. Further studies are needed, however, to elucidate the long-term impact of epicardial fat in this patient population.

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Conflicts of Interest

Dr. Bairey Merz has received consulting fees from SHL Telemedicine and iRhythm. Dr. Wei has received consulting fees from Abbott Vascular. The other co-authors do not report any conflict of interest.

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Table 1. Demographics and resting hemodynamics in women with suspected INOCA.

	Low Epicardial Fat	Medium Epicardial Fat	High Epicardial Fat	p-value
n	98	98	98	-
Age, years	52 ± 12	53 ± 10	56 ± 10[a,b]	**0.02**
Body mass index (BMI), kg/m^2	24 ± 4[b]	28 ± 6	31 ± 7[a,b]	**<0.001**
Body surface area (BSA), m^2	1.7 ± 0.2[b]	1.8 ± 0.2	1.9 ± 0.2[a,b]	**<0.001**
Hemodynamics				
Heart rate, bpm	65 ± 10	66 ± 10	69 ± 10[a]	**0.04**
Mean arterial pressure, mmHg	80 ± 12[b]	85 ± 13	88 ± 14[a]	**<0.001**
LVEDP, mmHg	11 ± 5[b]	13 ± 6	14 ± 7[a]	**0.01**
Medical History				
Hypertension	21 (21%)	38 (38%)	44 (44%)[a]	**0.002**
Diabetes	6 (6%)	10 (10%)	13 (13%)	0.22
Smoking	30 (30%)	36 (36%)	29 (29%)	0.11
Predicted max METs	8.2 ± 5.9	7.2 ± 5.3	7.1 ± 5.5	0.41
SAQ 7 score	55.8 ± 20.1	54.9 ± 22.1	55.2 ± 22.7	0.99
Coronary Function and Coronary Severity				
CFR	2.9 ± 0.7	3.0 ± 0.8	2.8 ± 0.7	0.55
Nitroglycerine diameter response	18.4 ± 20.9	17.5 ± 15.8	14.4 ± 15.1	0.58
Ach diameter response	-2.6 ± 17.5	2.2 ± 14.5	0.3 ± 14.6	0.46
CBF response to Ach	62.2 ± 86.7	67.8 ± 86.0	59.2 ± 76.1	0.69
Spasm	24 (24%)	13 (13%)	15 (15%)	0.09
Total coronary severity score	6.9 ± 3.4[b]	8.5 ± 4.2	8.5 ± 4.3[a]	**0.004**

Values expressed as mean ± SD.

Abbreviations: LVEDP (left ventricular end-diastolic pressure), SAQ (Seattle angina questionnaire), CFR (coronary flow reserve), Ach (Acetylcholine), CBF (coronary blood flow).

[a] $p < 0.05$ vs Low Epicardial Fat.

[b] $p < 0.05$ vs Medium Epicardial Fat.

Table 2. Four-chamber morphology and function analysis.

	Low Epicardial Fat	Medium Epicardial Fat	High Epicardial Fat	p-value
Left Ventricle				
EDV, mL/m^2	69.9 ± 10.5	69.1 ± 11.2	64.4 ± 10.9[a,b]	**0.002**
ESV, mL/m^2	26.5 ± 5.2	26.2 ± 7.0	25.0 ± 7.1[a]	**0.03**
SV, mL/m^2	43.3 ± 6.8	42.9 ± 6.6	39.9 ± 6.9[a,b]	**0.002**
EF, %	62.1 ± 4.1	62.3 ± 5.7	61.7 ± 7.0	0.66
Mass, g/m^2	41.3 ± 6.1	41.3 ± 4.8	43.3 ± 6.9[a]	0.06
Concentricity, g/mL	0.60 ± 0.08	0.61 ± 0.11	0.69 ± 0.14[a,b]	**<0.001**
Septal Thickness Diastole, mm	6.2 ± 0.8	6.5 ± 1.0	7.1 ± 1.2[a,b]	**<0.001**
Circumferential strain, %	-19.5 ± 1.7	-19.5 ± 2.3	-19.2 ± 2.5	0.61
Early diastolic strain rate, s^{-1}	0.88 ± 0.19	0.86 ± 0.18	0.79 ± 0.19[a,b]	**0.01**
Late diastolic strain rate, s^{-1}	0.58 ± 0.19	0.58 ± 0.16	0.62 ± 0.21	0.39
Early-to-late diastolic strain rate	1.68 ± 0.68	1.63 ± 0.69	1.47 ± 0.81[a]	**0.02**
Longitudinal strain, %	-20.2 ± 2.0	-19.0 ± 6.1	-18.8 ± 2.8[a]	**0.01**
Early diastolic strain rate, s^{-1}	0.87 ± 0.22	0.87 ± 0.22	0.79 ± 0.22[a,b]	**0.01**
Late diastolic strain rate, s^{-1}	0.74 ± 0.23	0.74 ± 0.21	0.81 ± 0.27	0.13
Early-to-late diastolic strain rate	1.31 ± 0.61	1.28 ± 0.53	1.09 ± 0.54[a,b]	**0.004**
Right Ventricle				
EDV, mL/m^2	69.1 ± 12.1	66.6 ± 10.7	63.0 ± 11.1[a,b]	**0.002**
ESV, mL/m^2	46.1 ± 13.2	44.6 ± 12.7	45.0 ± 13.2[a]	**0.03**
SV, mL/m^2	42.5 ± 7.0	41.8 ± 6.7	39.1 ± 7.1[a,b]	**0.01**
EF, %	61.7 ± 4.8	63.1 ± 6.1	62.2 ± 6.8	0.21
Longitudinal strain, %	-27.3 ± 3.4	-27.2 ± 3.6	-27.0 ± 3.7	0.97
Early diastolic strain rate, s^{-1}	1.08 ± 0.27	1.09 ± 0.29	0.93 ± 0.28[a,b]	**<0.001**
Late diastolic strain rate, s^{-1}	1.20 ± 0.35	1.22 ± 0.41	1.39 ± 0.45[a,b]	**0.01**
Early-to-late diastolic strain rate	0.98 ± 0.39	1.06 ± 0.74	0.73 ± 0.29[a,b]	**<0.001**
Left Atrium				
Max volume, mL/m^2	37.4 ± 10.9	36.0 ± 10.3	35.4 ± 9.8	0.53
EF, %	0.61 ± 0.08	0.59 ± 0.08	0.58 ± 0.09[a]	**0.03**
Conduit Fraction, %	0.34 ± 0.10	0.32 ± 0.08	0.28 ± 0.10[a,b]	**<0.001**
Reservoir strain, %	22.8 ± 3.8	22.2 ± 3.6	21.9 ± 4.2	0.24
Conduit strain, %	13.6 ± 4.1	12.8 ± 3.5	12.1 ± 3.6[a]	**0.04**
Reservoir strain rate, s^{-1}	0.98 ± 0.26	0.92 ± 0.23	0.87 ± 0.21[a]	**0.01**
Conduit strain rate, s^{-1}	-1.15 ± 0.44	-1.04 ± 0.30	-1.00 ± 0.34[a]	**0.04**

Values expressed as mean ± SD.

Abbreviations: EDV (end-diastolic volume), ESV (end-systolic volume), SV (stroke volume), EF (ejection fraction).

[a] p< 0.05 vs Low Epicardial Fat.
[b] p< 0.05 vs Medium Epicardial Fat.

Table 3: Relations between epicardial fat and cardiac morphology and function endpoints.

	Not adjusted		Adjusted for Age & BMI & Hypertension	
	Unadjusted beta (β)	**p-value**	**Adjusted beta (β)**	**p-value**
Left Ventricle				
EDV, mL/m^2	-0.19	**0.002**	-0.06	0.39
ESV, mL/m^2	-0.11	0.06	-0.04	0.59
SV, mL/m^2	-0.15	**0.01**	-0.04	0.55
EF, %	0.02	0.73	0.03	0.71
Mass, g/m^2	0.18	**0.003**	0.10	0.13
Concentricity, g/mL	0.33	**<0.001**	0.15	**0.01**
Septal Thickness Diastole, mm	0.39	**<0.001**	0.17	**0.002**
Circumferential strain, %	0.05	0.42	0.03	0.64
Early diastolic strain rate, s^{-1}	-0.21	**<0.001**	-0.08	0.27
Late diastolic strain rate, s^{-1}	0.08	0.17	0.03	0.63
Early-to-late diastolic strain rate	-0.14	**0.02**	0.00	0.99
Longitudinal strain, %	0.14	**0.02**	0.05	0.53
Early diastolic strain rate, s^{-1}	-0.15	**0.01**	-0.04	0.59
Late diastolic strain rate, s^{-1}	0.13	**0.04**	0.11	0.09
Early-to-late diastolic strain rate	-0.19	**0.001**	-0.08	0.21
Right Ventricle				
EDV, mL/m^2	-0.18	**0.003**	-0.08	0.23
ESV, mL/m^2	-0.16	**0.01**	-0.10	0.13
SV, mL/m^2	-0.14	**0.02**	-0.04	0.59
EF, %	0.07	0.24	0.09	0.17
Longitudinal strain, %	0.01	0.85	-0.07	0.37
Early diastolic strain rate, s^{-1}	-0.23	**<0.001**	-0.07	0.32
Late diastolic strain rate, s^{-1}	0.15	**0.02**	0.14	0.05
Early-to-late diastolic strain rate	-0.19	**0.002**	-0.12	0.10
Left Atrium				
Max volume, mL/m^2	-0.06	0.34	0.03	0.72
EF, %	-0.15	**0.02**	-0.08	0.26
Conduit Fraction, %	-0.24	**<0.001**	-0.15	**0.02**
Reservoir strain, %	-0.09	0.16	-0.01	0.85
Conduit strain, %	-0.15	**0.02**	-0.06	0.40
Reservoir strain rate, s^{-1}	-0.21	**<0.001**	-0.12	0.12
Conduit strain rate, s^{-1}	0.15	**0.02**	0.06	0.39

Values expressed as mean ± SD.

Abbreviations: EDV (end-diastolic volume), ESV (end-systolic volume), SV (stroke volume), EF (ejection fraction).
β represents standardized beta coefficients.
$p < 0.05$ indicates statistical significance.

Supplementary Material

Pericardial fat is composed of two distinct adipose depots: (1) epicardial fat, which is a metabolically active adipose tissue located between the heart and the pericardium, and (2) paracardial fat, which is the fat deposit in the mediastinum outside of the parietal pericardium. Both depots are visible on the horizontal long axis cardiac magnetic resonance (CMR) cine (i.e., four chamber view), offering an attractive opportunity to quantify pericardial fat from standard CMR cine images. The validity of this approach, however, remains incompletely understood.

We leveraged 25 cases from the Women's Ischemia Syndrome Evaluation - Coronary Vascular Dysfunction Continuation cohort who underwent both cardiac MRI and cardiac CT within a median of 35 days apart. For MRI, pericardial fat area was measured from a single high resolution steady state free precession cine image in the horizontal long axis imaging plane using commercially available software (CVI42 V5.13.5, Circle Cardiovascular Imaging, Figure Panel A). For CT, pericardial fat volume was measured using a fully automated deep learning algorithm (QFAT 2.0, Figure Panel A).

The fat area measured from a single horizontal long-axis cine image exhibited a close association with fat volume measured by three-dimensional cardiac CT, showing strong correlations for epicardial fat (R^2=0.72, p<0.01, Figure Panel B), paracardial fat (R^2=0.80, p<0.01, Figure Panel C), and pericardial fat (R^2=0.91, p<0.01, Figure Panel D).

Measuring pericardial fat area, and its constituent parts, from a single horizontal long axis cine image is both feasible and strongly related to reference standard pericardial fat volume by cardiac CT.

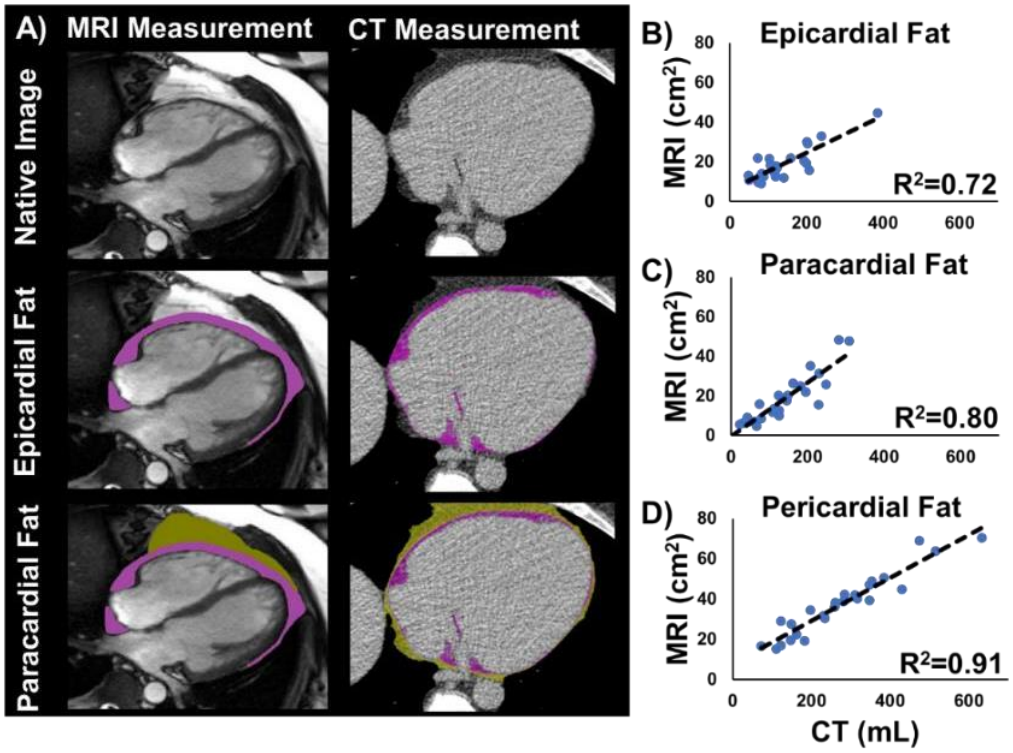

Figure. (A) *Top Left:* Representative horizontal long axis cine images. *Top Right:* Representative axial non-contrast-enhanced CT image. *Middle:* Epicardial fat highlighted in purple. *Bottom:* Paracardial fat highlighted in green. **(B)** Relationship between epicardial fat area measured by MRI and epicardial fat volume measured by CT. **(D)** Relationship between pericardial fat area measured by MRI and pericardial fat volume measured by CT.

Chapter 3

Excess Pericardial Fat is Related to Adverse Cardio-Mechanical Interaction in Heart Failure with Preserved Ejection Fraction

A version of this chapter has been published: Sauyeh K. Zamani, Satyam Sarma, James P. MacNamara, Linda S. Hynan, Mark J. Haykowsky, Christopher M. Hearon, Denis Wakeham, Tiffany Brazile, Benjamin D. Levine, Vlad G. Zaha, Michael D. Nelson. Excess Pericardial Fat is Related to Adverse Cardio-Mechanical Interaction in Heart Failure with Preserved Ejection Fraction. *Circulation.* 2023; 148(18): 1410-1412.
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Heart failure with preserved ejection fraction (HFpEF) is the fastest growing form of HF, found predominantly in older persons. The primary chronic symptom in HFpEF is severe exercise intolerance, contributing to reduced quality of life.[1] In the United States, the majority of HFpEF patients are overweight/obese.[2] While numerous pathophysiological links exist between obesity and HFpEF, emerging evidence suggests that excess adiposity—particularly surrounding the heart—may uniquely contribute to diastolic dysfunction and high left sided filling pressures.[3] Excess adiposity surrounding the heart may be physically constraining, and contribute to ventricular interdependence; a process of mechanical interaction between the right and left ventricle due to dynamically increased right sided pressures and the confines of the pericardial space.[4] Evidence for this pathophysiology, however, remains limited to observations from a single group, using transthoracic echocardiography, under resting conditions.[3] Given the potential for exercise to exacerbate cardio-mechanical interaction, due to increases in venous return by way of the skeletal muscle and respiratory pumps, we evaluated the relationship between pericardial fat and cardio-mechanical interaction in HFpEF using cardiac magnetic resonance imaging (cMRI) at rest and during dynamic exercise.

Twenty-eight individuals with HFpEF (17F, BMI: 37±7 kg/m^2, age: 70±6 years) provided written informed consent to participate; approved by the University of Texas Southwestern Medical Center Institutional Review Board. Participants were recruited to a clinical trial studying mechanisms of exercise intolerance in HFpEF (NCT04068844). Inclusion criteria were: ≥55 years of age, clinical symptoms of heart failure, ejection fraction >50% and objective evidence of volume overload, including either heart failure hospitalization requiring intravenous diuretics, pulmonary edema by chest x-ray, elevated N-terminal pro-B-type natriuretic peptide >900

pg/mL, or elevated left ventricular end-diastolic pressure or PCWP >16 mm Hg. Exclusion criteria included hereditary or infiltrative cardiomyopathy, previous ejection fraction <50%, body mass index >55 kg/m^2, regular use of phosphodiesterase inhibitors, left bundle branch block, chronic kidney disease stage 4 or greater, severe pulmonary disease, and severe valvular disease. The data included herein are available from the corresponding author on reasonable request.

Cardiac MRI was performed using a 3T Philips Achieva scanner. Cardiac morphology and function were assessed using ECG-gated cine images, acquired at end-expiration. Epicardial and paracardial fat area were measured using the horizontal long-axis image (**Figure 1A**), with epicardial fat defined as the adipose tissue within the pericardium and paracardial fat defined as the adipose tissue outside of the pericardium; the sum of which was defined as pericardial fat. To assess ventricular interdependence, short-axis real-time (ungated) free-breathing cine images were acquired at rest and during dynamic leg exercise (30 Watts) using an MRI-compatible ergometer (Ergospect, Austria). Ventricular interdependence was defined by the LV eccentricity index, calculated as the ratio of the LV short-axis diameter parallel to the septum (anteroposterior dimension, AP) to the LV short-axis diameter perpendicular to the septum (septolateral dimension, SL) at end-diastole and end-inspiration (**Figure 1A**).[3] Values >1.0 indicate septal flattening, enhanced ventricular interdependence, and increased pericardial constraint. Subcutaneous and visceral fat area were assessed at the L2/L3 region, using a modified DIXON water-suppressed image (Slice-O-Matic, Montreal).

At rest, adverse cardio-mechanical interaction (i.e., AP/SL >1.0) was observed in 13 of the 28 cases. In those with adverse cardio-mechanical interaction, both epicardial and paracardial fat area were significantly higher (**Figure 1B**), as was visceral fat area (224.2±80.3 vs. 309.0±79.9 cm^2,

p=0.03) and mean resting pulmonary artery pressure (16.6±3.6 vs. 21.8±6.1 mmHg, p=0.01). No differences in LV or RV volumes (LVEDV: 72.4±19.2 vs. 73.8±14.0 mL/m^2, RVEDV: 72.0±15.5 vs. 73.2±11.5 mL/m^2, respectively), BMI (35±7 vs. 39±6 kg/m^2, p=0.16), subcutaneous fat area (312.1±154.4 vs. 344.6±125.9 cm^2, p=0.62), VO_{2max} (14.2±5.4 vs. 12.3±4.2 ml/kg/min, p=0.33), PCWP (11.5±4.3 vs. 14.4±4.2 mmHg, p=0.10), or pulmonary vascular resistance (PVR; 2.4±1.9 vs. 3.2±1.1 WU, p=0.25) were observed between groups.

Consistent with prior reports, epicardial fat was strongly related to LV eccentricity index. Unique to this study, paracardial fat was also strongly related to LV eccentricity index, which helped to drive the relationship between pericardial fat and LV eccentricity index (**Figure 1C**). Importantly, LV eccentricity was not related to BMI, subcutaneous fat, visceral fat, or PVR (**Figure 1D**). Exercise did not exacerbate cardio-mechanical interaction (**Figure 1E**).

Together, these data extend prior reports of adverse cardio-mechanical interaction in obese HFpEF. Strengths of this investigation include the high-resolution cMR imaging and ability to differentiate cardiac adipose tissue compartments. That abdominal fat did not significantly influence the relationship between pericardial fat and cardio-mechanical interaction, and the limited role pulmonary vascular resistance appears to be playing, highlights the importance of excess cardiac adiposity in driving these observations. That dynamic exercise did not exacerbate cardio-mechanical interaction likely reflects the supine body position of our participants. More work is therefore needed to evaluate ventricular interdependence during upright exercise, and the impact that reducing cardiac adiposity has on this relationship. Indeed, a reduction in epicardial fat following bariatric surgery improves ventricular interdependence at rest.[5]

Figure Legend

Figure. (A) *Left:* Representative high resolution horizontal long axis cine image from a case with mild-to-moderate pericardial fat *(Top*)*,* and a case with high pericardial fat *(Bottom*)*. Middle:* Real-time free breathing short axis images showing normal cardio-mechanical interaction *(Top),* and adverse cardio-mechanical interaction *(Bottom*) in each of the respective cases*. Right:* Schematic representation illustrating the method by which LV eccentricity index was evaluated (LV eccentricity index = AP/SL). **(B)** Group data illustrating greater epicardial fat area (*top*) and paracardial fat area (*bottom*), in cases with abnormal LV eccentricity (red bar) versus those cases with normal LV eccentricity (blue bar). **(C)** Relationship between epicardial fat (*left)*, paracardial fat (*middle*) and pericardial fat (*right)* and LV eccentricity index at rest. Notably, adjusting for total abdominal fat (visceral + subcutaneous fat) did not significantly influence the relationships. Blue circles represent cases with LV eccentricity index ≤ 1, red circles represent cases with LV eccentricity index > 1. **(D)** Relationship between BMI (n=28), subcutaneous fat (n=20), visceral fat (n=21), and pulmonary vascular resistance (n=23) and LV eccentricity index at rest. Blue circles represent cases with LV eccentricity index ≤ 1, red circles represent cases with LV eccentricity index > 1. **(E)** *Left:* Photograph illustrating our MRI compatible exercise ergometer which allowed participants to exercise at 30W during dynamic image acquisition. *Right:* LV eccentricity index at rest to during exercise. Blue lines represent cases with LV eccentricity index ≤ 1, red lines represent cases with LV eccentricity index > 1.

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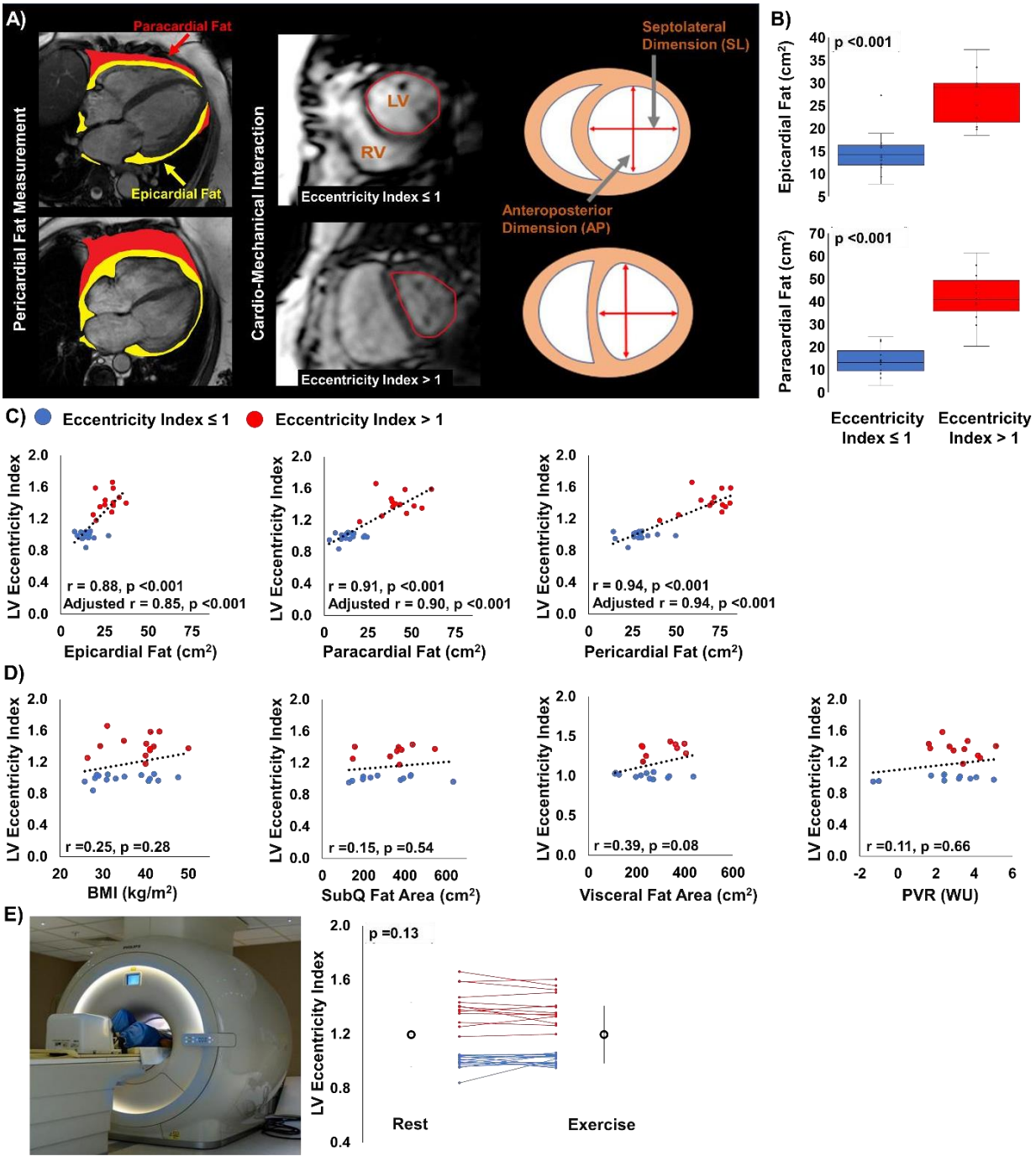
Conflict of Interest Disclosures

None.


A)
Paracardial Fat
Epicardial Fat
Pericardial Fat Measurement
Cardio-Mechanical Interaction
LV
RV
Eccentricity Index ≤ 1
Eccentricity Index > 1
Septolateral Dimension (SL)
Anteroposterior Dimension (AP)
B)
p <0.001
Epicardial Fat (cm²)
p <0.001
Paracardial Fat (cm²)
Eccentricity Index ≤ 1
Eccentricity Index > 1
C)
Eccentricity Index ≤ 1
Eccentricity Index > 1
LV Eccentricity Index
r = 0.88, p <0.001
Adjusted r = 0.85, p <0.001
Epicardial Fat (cm²)
r = 0.91, p <0.001
Adjusted r = 0.90, p <0.001
Paracardial Fat (cm²)
r = 0.94, p <0.001
Adjusted r = 0.94, p <0.001
Pericardial Fat (cm²)
D)
r =0.25, p =0.28
BMI (kg/m²)
r =0.15, p =0.54
SubQ Fat Area (cm²)
r =0.39, p =0.08
Visceral Fat Area (cm²)
r =0.11, p =0.66
PVR (WU)
E)
p =0.13
Rest
Exercise

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Chapter 4

Pericardial Fat Across the Spectrum of Health and Disease

1. Introduction

Obesity is a significant risk factor for cardiovascular diseases. According to the World Health Organization, worldwide adult obesity has more than doubled since 1990, and adolescent obesity has quadrupled.[1] While body mass index (BMI) is commonly used to diagnose overall obesity, it does not adequately capture the extent or distribution of fat within the body. This distinction is crucial because visceral adiposity (fat around internal organs) significantly increases the risk of developing heart failure.[2, 3]

Of particular interest is the total fat surrounding the heart, collectively known as pericardial fat, which has garnered attention for its potential role in the pathophysiology of heart failure.[4] Pericardial fat is composed of two distinct depots: (1) epicardial adipose tissue (EAT), a metabolically active adipose tissue located between the myocardium and the visceral layer of the pericardium, directly covering the heart, and (2) paracardial adipose tissue (PAT), the fat deposit in the mediastinum outside of the parietal pericardium.[5]

High levels of pericardial fat, encompassing both EAT and PAT, pose significant risks to cardiovascular health. EAT secretes pro-inflammatory cytokines and adipokines, which induce local inflammation and promote atherosclerosis in the coronary arteries.[6] Its proximity to the heart also allows EAT to potentially impair cardiac function, contributing to conditions such as heart failure with preserved ejection fraction (HFpEF).[7] In contrast, PAT does not share these properties. Biochemically, EAT and PAT are different. There is robust evidence that EAT functions as an active endocrine organ[8, 9], whereas the role of PAT in secreting adipokines remains unclear.

This review comprehensively delineates the pathophysiology of pericardial fat, current treatment approaches, and future directions concerning the involvement of pericardial fat across the spectrum of health and disease.

2. Anatomy and Physiology of Pericardial Fat

EAT is predominantly found along the distribution of the coronary arteries, over the right ventricle, and at the apex. There is three to four times more EAT associated with the right ventricle than with the left.[5, 10]

As mentioned, EAT secretes bioactive molecules, including adipokines and pro-inflammatory cytokines, which play a crucial role in the development of inflammation.[11] Key among these agents are interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and monocytes chemoattractant protein-1 (MCP-1). Due to its location, EAT shares the same coronary microcirculation with the myocardium.[12] These molecules can exert paracrine effect and diffuse into the myocardium and coronary arteries, increasing oxidative stress, recruiting inflammatory cells, and promoting local inflammation, thereby contributing to the pathogenesis of cardiovascular diseases.[13, 14] In contrast, the role of PAT in adipokines secretion remain unclear, necessitating further research to determine whether it similarly contributes to systemic physiology or exhibit distinct biochemical characteristics that warrant separate investigation.

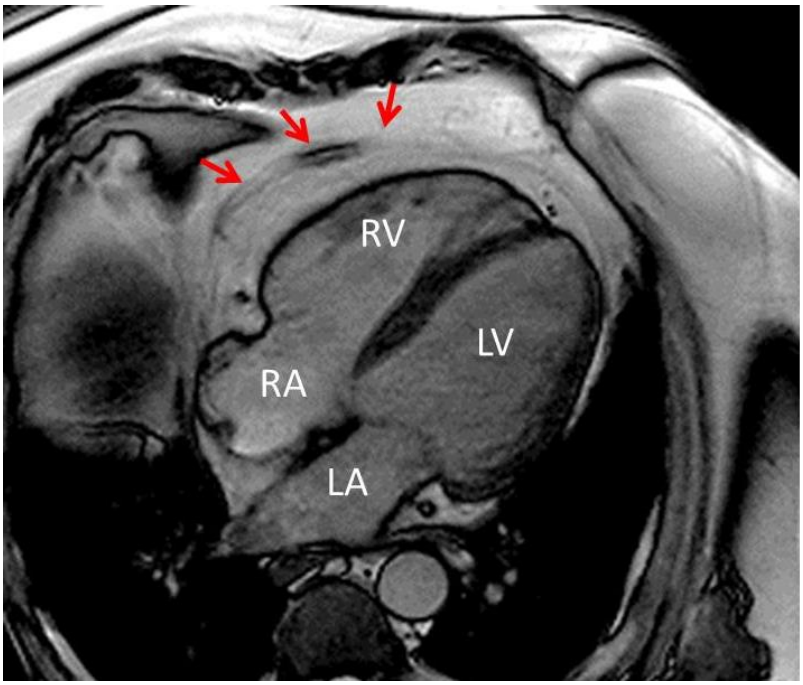

Figure 1. The distribution of epicardial adipose tissue (EAT) around the right ventricle in a horizontal long-axis cine view using MRI. The red arrows indicate the pericardium. LV, left ventricle; RV, right ventricle; LA, left atrium; RA, right atrium.

3. Imaging and measurement of Pericardial fat

Over the last decade, imaging studies have identified pericardial fat as a measurable risk factor for cardiovascular disease. These studies have utilized various techniques, including Computed Tomography (CT) scans, Echocardiography, and Magnetic Resonance Imaging (MRI). The measurement of EAT is sensitive to the phase of the cardiac cycle, requiring specific measurements at either end-diastole or end-systole. At end-diastole, EAT is compressed, while at end-systole, the fat is stretched due to the systolic function, resulting in maximum EAT thickness. In contrast, PAT exhibits minimal thickness changes throughout the cardiac cycle.[15]

3.1 Computed Tomography (CT)

Computed Tomography (CT) is a specialized medical imaging technique that generates images by rotating an X-ray source and detectors around the person, emitting X-rays through the body from multiple angles. As the X-rays pass through the body, detectors measure their intensity, creating data that is sent to a computer. The computer uses advanced algorithms to reconstruct cross-sectional images (slices) of the scanned area, which are then displayed on a monitor. This process allows for detailed visualization of bones, organs, and tissues in the body. CT scans are valuable for diagnosing a wide range of medical conditions due to their ability to provide clear, detailed images quickly and effectively.

CT scans are a highly effective method for measuring pericardial fat due to their high spatial resolution and detailed imaging capabilities. This imaging modality allows for precise quantification of EAT volume and distribution, which is crucial for assessing cardiovascular risk.[16] CT scans provide consistent and reproducible measurements, making them a reliable took in clinical settings. However, a significant limitation of CT is the exposure to ionizing radiation, which can be a concern, particularly for patients requiring multiple scans. Additionally, CT scans are relatively expensive and may not be available in all healthcare facilities. Despite these drawbacks, the detailed imaging and quantification capabilities make CT a valuable tool in cardiovascular research and clinical practice.

3.2 Echocardiography

Echocardiography generates images using ultrasound waves, a non-invasive technique that captures real-time images of the heart's structures and blood flow. A transducer emits high-

frequency sound waves into the chest, which then bounce off the heart's tissues and return as echoes. These echoes are detected by the transducer and converted into electrical signals, which are processed by a computer to create moving images of the heart. By analyzing the frequency and timing of the echoes, echocardiography produces detailed visualizations of the heart's chambers, valves, and blood flow patterns. This real-time imaging capability allows to assess cardiac function, detect abnormalities, and monitor treatment, making echocardiography a versatile tool in cardiovascular diagnostics.

Echocardiography is a widely available and commonly used imaging technique for assessing pericardial fat. It utilizes ultrasound waves, thereby avoiding the risks associated with ionizing radiation present in CT scans. Echocardiography provides real-time visualization of the heart, allowing for dynamic assessment of cardiac structures and function.[17] One of the primary advantages of echocardiography is its accessibility and lower cost compared to other imaging modalities such as CT scans and MRI. However, echocardiography has lower spatial resolution, which may limit the accuracy of pericardial fat measurements. Additionally, the quality of the images obtained can be highly dependent on the skill and experience of the operator, making it somewhat less consistent than other methods. Despite these limitations, echocardiography remains a valuable, non-invasive tool for initial assessments and routine follow-up in clinical settings to evaluate cardiovascular risk.[18, 19]

3.3 Magnetic Resonance Imaging (MRI)

Magnetic resonance imaging (MRI) generates images using a combination of strong magnetic field and radio waves. When a patient lies inside the MRI machine, the magnetic field

aligns hydrogen atoms within the body's tissues. Radio waves are then pulsed through the body, causing these aligned atoms to emit signals. Detectors in the MRI machine capture these signals, which vary depending on the type of tissue they come from and their location within the magnetic field. A computer processes these signals to construct detailed cross-sectional images of the body's internal structures. The resulting MRI images provide clear, high-resolution views of organs, soft tissues, and even subtle changes in anatomy or pathology, making MRI a powerful took for diagnosing a wide range of medical conditions without using ionizing radiation.

Magnetic Resonance Imaging (MRI) is an advanced imaging modality that offers excellent soft tissue contrast and high spatial resolution, making it ideal for detailed assessments of pericardial fat.[20] MRI does not involve ionizing radiation, which is a significant advantage, especially for repeated imaging studies. It provides comprehensive information about cardiac structures, function, and tissue characteristics, allowing for thorough evaluations of cardiovascular health.[21] To validate the accuracy and reliability of these imaging modalities in clinical practice, van Woerden et al. conducted a study demonstrating a significant correlation between EAT volume using MRI and EAT thickness assessed by echocardiography.[22] However, MRI is relatively expensive and time-consuming compared to other imaging techniques. Accessibility can also be an issue, as MRI machines are not available in all healthcare settings. Additionally, MRI may not be suitable for all patients, such as those with certain metal implants, severe claustrophobia, or obesity. Obesity can present challenges for MRI due to narrow bore of the machine, which may not comfortably accommodate larger individuals, potentially affecting positioning and image quality. Despite these limitations, MRI's detailed imaging capabilities and safety profile make it a preferred method for in-depth cardiac studies.

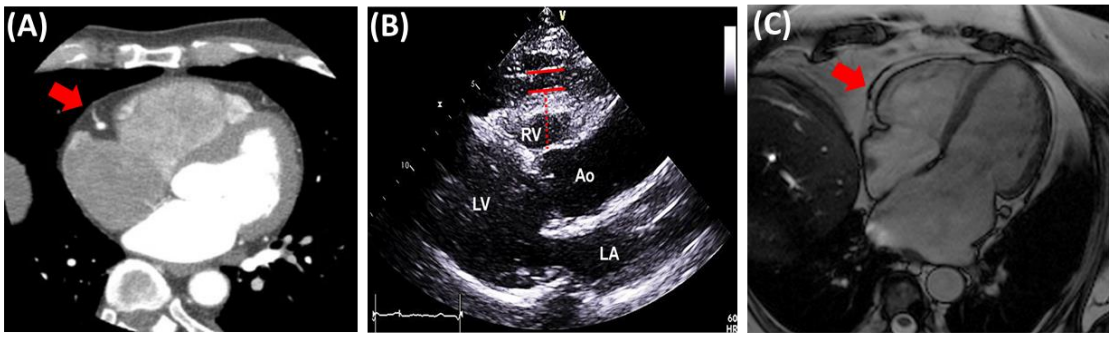

Figure 2. Three distinct imaging techniques for evaluating EAT. **(A)** Contrast-enhanced Computed Tomography image in the horizontal long-axis image. Adapted with permission from Siriapisith T. et al. A 3D deep learning approach to epicardial fat segmentation in non-contrast and post-contrast cardiac CT images. PeerJ Comput Sci. 2021. DOI: 10.7717/peerj-cs.806. **(B)** Echocardiography image in the parasternal long-axis orientation. Used with permission from Rhee TM. et al. Association between epicardial adipose tissue thickness and parameters of target organ damage in patients undergoing coronary angiography. Hypertens Res. 2019. DOI: 10.1038/s41440-018-0180-8. **(C)** Original image from our lab database on a magnetic resonance image in the horizontal long-axis view. The red marks indicate epicardial fat.

4. Sex-Specific Differences in Pericardial Fat Accumulation

There is a significant difference in the cardiovascular disease risk between men and women.[23] This disparity has been attributed to declining estrogen levels in women post menopause, which lead to various metabolic changes promoting fat redistribution and accumulation, particularly around the abdomen and heart.[24] EAT thickness does not differ by sex in patients younger than 60 years; however, post-menopausal women aged over 60 years tend to have greater EAT thickness compared to men in the same age group.[25]

Additionally, research by Khoudary et al. suggests that increased EAT volume is linked to coronary artery calcification.[26] However, the correlation between coronary artery calcification and PAT volume appears to be influenced by menopausal status and lower estradiol levels. This highlights PAT as a potential marker for coronary artery disease specific to menopause, underscoring the importance of separately assessing EAT and PAT as distinct fat deposits. Currently, there is a lack

of information regarding the role of PAT in sex-specific differences. While studies have extensively examined the endocrine functions of EAT, the specific contributions of PAT to metabolic and inflammatory processes in men and women remain unclear. Further research is needed to elucidate whether PAT exhibits sex-specific variations in its biochemical and physiological roles.

5. Pericardial Fat and Oxygen Supply

Studies suggest that as adipose tissue expands, the proportion of cardiac output supplying that tissue does not increase.[27] Moreover, blood flow to adipose tissue following a meal is lower in obese individuals compared to lean individuals.[28] Pasarica et al showed that oxygen partial pressure of abdominal adipose tissue was lower in obese participants compared to lean participants and was negatively correlated with percentage of body fat. Interestingly, compared with lean participants, obese participants had 44% lower capillary density and 58% lower vascular endothelial growth factor, suggesting adipose tissue rarefaction (capillary drop out). Of clinical importance, adipose tissue oxygen partial pressure negatively correlated with macrophage inflammatory protein secretion, suggesting that lower adipose tissue oxygen partial pressure could drive adipose tissue inflammation in obesity. It is concluded that as adipose tissue accumulates, angiogenesis appears to be compromised during obesity.[29] These observations suggest that adipose tissue may experience hypoxia.[30]

During a hypoxic state, adipocytes begin to release pro-inflammatory cytokines, leading to the migration of immune cells into the adipose tissue.[9] A study by Obata et al. showed that mitochondrial respiratory capacity in EAT was impaired in patients with coronary artery disease and correlated with the severity of coronary artery stenosis.[31] These findings support the idea

that mitochondrial dysfunction in EAT contributes to the progression of coronary atherosclerosis. Further research is needed to expand on specific mechanisms underlying adipose tissue hypoxia, particularly in PAT. Exploring how PAT responds to hypoxic conditions and its implications for cardiovascular health could provide valuable insights.

6. Pericardial Fat in HFpEF

Heart failure represents a complex clinical syndrome characterized by a rapidly increasing incidence among cardiovascular diseases.[32] Studies have stablished a significant and independent link between obesity and the development of HFpEF.[33-37] In particular, visceral fat plays a crucial role in cardiovascular disease and the progression of heart failure.[2] Notably, visceral fat has been associated with the development of heart failure, whereas subcutaneous fat shows no such correlation.[36] Of particular concern is EAT, which has been linked to metabolic syndrome,[19, 38] atrial fibrillation,[39, 40] coronary atherosclerosis,[6, 41] and HFpEF.[4, 7, 42, 43] Emerging evidence suggests that excess adiposity, particularly EAT, may uniquely contribute to diastolic dysfunction, increased left-sided filling pressures, left ventricular hypertrophy, increase cardio-mechanical interaction, and exercise intolerance in HFpEF patients.[4, 7, 44]

The challenge lies in the multifactorial nature of HFpEF, which is often accompanied by various comorbidities such as coronary artery disease, type II diabetes, obesity, and hypertension.[45] These conditions are highly prevalent and frequently coexist in HFpEF patients, complicating the identification of the specific role of EAT in the pathophysiologic mechanism of HFpEF. However, a study by Sicari R et al. showed that in obese HFpEF patients, pericardial fat exhibited a strong correlation with metabolic syndrome, while no such correlation was found with EAT alone.[46]

Consequently, pericardial fat was associated with cardiovascular risk factors, including increased visceral fat accumulation, elevated blood pressure, insulin resistance, and abnormal lipid levels.

Excessive adipose tissue around the heart can physically restrict it and contribute to ventricular interdependence, a process involving mechanical interaction between the right and left ventricles due to dynamically increased right-sided pressures and the confines of the pericardial space.[4] Interestingly, in patients with HFpEF, PAT strongly correlates with the left ventricular eccentricity index.[44] It is important to note that in this patient group, left ventricular eccentricity was not associated with body mass index, subcutaneous fat, visceral fat, or pulmonary vascular resistance. Further research is needed to better understand how PAT contribute to HFpEF patients.

7. Pericardial Fat in HFrEF

Obesity is a well-established major risk factor for the development of HFpEF.[3, 47] Conversely, initial studies have described a surprising paradoxical relationship between high BMI and ejection fraction in HFrEF patients, indicating that those with mild obesity experience significant improvements in ejection fraction compared to individuals with either lower or higher BMI.[48-50] However, several caveats should be considered in interpreting this paradox as it relates to heart failure. Most of these studies have focused on BMI, which does not count for the location or amount of body fat. Additionally, retained fluid can contribute to body weight in heart failure patients. Consequently, alternative anthropometric indices, such as waist circumference, waist-to-hip ratio, and DEXA, have been proposed to better reflect the distribution of body fat and total fat mass.[51-53]

Emerging evidence suggests that EAT influences HFrEF and HFpEF in distinct ways. A study by Pugliese NR et al. demonstrated that elevated EAT levels in HFrEF patients are associated with lower natriuretic peptides, troponin T, and C-reactive protein. In contrast, this protective association is absent in HFpEF, where elevated EAT is linked to adverse outcomes. Furthermore, it was shown that in HFpEF patients, higher EAT levels correspond to a lower risk of cardiovascular death and heart failure hospitalization, while in HFrEF patients, reduced EAT is associated with a worse prognosis.[54] The exact molecular pathways underlying the different effects of EAT in HFrEF and HFpEF have yet to be investigated. Further research is essential to determine if PAT uniquely contributes to HFrEF patients.

8. Pericardial Fat in coronary artery disease

Coronary artery disease (CAD) encompasses a spectrum of conditions where the coronary arteries which supply oxygen-rich blood to the cardiomyocyte, are affected by atherosclerosis, the buildup of plaque consisting of cholesterol, fat, and other substances. In typical cases of CAD, this plaque accumulation leads to narrowing or blockage within the arteries, reducing blood flow and potentially causing symptoms like chest pain (angina) or, in severe cases, heart attacks.[55] However, not all cases of CAD present with significant arterial blockages. Some individuals exhibit symptoms suggestive of CAD despite angiograms showing minimal or no obstructive disease. This variant is known as ischemia with no-obstructive coronary artery disease (INOCA). Rather than significant plaque buildup causing narrowing, non-obstructive CAD often involves abnormalities in the smaller coronary arteries or dysfunction of inner lining (endothelium) of the blood vessels.[56] These abnormalities can impair the ability of the coronary arteries to dilate or constrict appropriately in response to changing demands, such as during physical exertion or stress.

Diagnosing INOCA requires specialized testing beyond standard coronary angiography, which include coronary reactivity testing that assess the function rather than just the structure of the coronary arteries. These tests help identify abnormalities in coronary microvascular function or endothelial dysfunction, which underlies the symptoms experienced by patients.

Research from the NHLBI-Sponsored Women's Ischemia Syndrome Evaluation (WISE) study suggests that most women presenting with signs and symptoms of ischemia have no obstructive coronary artery disease (INOCA).[57] These women are at increased risk of developing HFpEF.[58] However, despite our growing understanding, the pathophysiologic mechanisms driving heart failure progression in INOCA remains incompletely understood. Consistent with the HFpEF phenotype, INOCA often involves left ventricular diastolic dysfunction and left atrial stiffness.[59-63] The association between EAT and cardiac function and coronary vascular function in INOCA patients is not well understood. Research indicates that in INOCA, elevated EAT correlates with impaired myocardial flow reserve, cardiometabolic risk factors, inflammation, and plaque vulnerability. Conversely, no link has been observed between increased EAT and myocardial ischemia.[64, 65] A limitations of these studies is the need to test for invasive vasospasm, as the prevalence of myocardial ischemia may be underestimated.

Less is known about the relationship between EAT and coronary vascular function, as well as its impact on cardiac morphology and function, which remains incompletely understood. In addition, further studies are required to support the predictive value of EAT levels as indicators of INOCA. Additionally, investigations are needed to determine whether EAT attenuation serves as superior risk predictors in patients with INOCA. These studies could include longitudinal follow-ups to better understand the progression of INOCA and its transition to HFpEF. Further research

is also essential to determine if PAT uniquely contributes to INOCA patients. Investigating the specific mechanisms by which PAT influences heart failure progression could provide valuable insights.

9. **Therapeutic Interventions Targeting Pericardial Fat**

9.1 Bariatric surgery

A study by Sorimachi H et al. demonstrated that following bariatric surgery, obese patients experienced a 22% decrease in BMI after 5.3 years, accompanied by favorable reductions in blood pressure, fasting glucose levels, and left ventricular remodeling. Additionally, visceral adipose tissue area decreased by 30%, and EAT was reduced by 14%. While left and right ventricular longitudinal strain improved, left atrial strain deteriorated, with left atrial volume and estimated left atrial pressure increasing.

Another study by Jamaly S et al. indicated that weight loss subsequent to bariatric surgery correlated with a 35% lower risk of developing heart failure over a 22-year follow-up period.[66] Bariatric surgery significantly reduces EAT level.[67-69] Given that EAT level is typically higher in HFpEF patients compared to controls, it is speculated that the decreased risk of heart failure post-surgery may be attributed to a localized reduction in EAT levels.

9.2 Pharmacological Interventions

Pharmaceutical interventions can modify EAT through various mechanisms. Statins, commonly used for lowering cholesterol, have been shown to reduce EAT, likely due to their anti-inflammatory properties.[70-72] Glucagon-like-peptide-1 (GLP-1) agonists, used in diabetes

management, also reduce EAT by improving insulin sensitivity and promoting weight loss.[73] Sodium-glucose co-transporter inhibitors (SGLT2i), primarily used in diabetes management, have been shown to reduce EAT.[74, 75] These drugs lead to weight loss and improved metabolic profiles. The reduction in EAT with SGLT2 inhibitors is likely due to their ability to enhance fat oxidation and improve insulin sensitivity, together helping to decrease EAT store.

9.3 Hormonal Changes

Menopause involves significant hormone shifts, notably a decline in estrogen levels. Estrogen is crucial for regulating fat distribution and metabolism. During menopause, the reduction in estrogen level leads to a redistribution of fat storage from peripheral to central areas of the body, including EAT. Research indicates that postmenopausal women tend to have higher volumes of central fat compound to premenopausal women, regardless of age or obesity status.[76] However, hormone therapy including oral conjugated equine estrogens could potentially attenuate the accumulation of EAT in menopausal women.[77, 78]

9.4 Diet

Lifestyle management, particularly diet, can suppress the accumulation of EAT and improve the clinical symptoms and prognosis of heart failure. Iacobellis G et al. showed that twenty severely obese individuals (BMI: 45 ± 5 kg/m^2) experienced a 32% reduction in EAT thickness, along with improvements in left ventricular mass and diastolic dysfunction, after six months of very low-calorie diet.[79] They demonstrated for the first time that cardiac changes correlated better with EAT changes than with BMI changes.

9.5 Exercise

Exercise training has been confirmed to significantly reduce EAT thickness and improve cardiac function. Serrano-Ferrer J et al. found that moderate to high intensity resistance or aerobic training significantly reduced EAT thickness and improved left ventricular longitudinal strain and strain rate as measured by echocardiography.[80] Another study by Honkala SM et al. reported that two weeks of continuous high-intensity interval training and moderate-intensity continuous training effectively reduced EAT volume and pericardial fat, as measured by CT scans, in both healthy individuals and patients with defective glucose tolerance.[81] As a result of these studies, suppressing abnormal EAT expansion may be a promising therapeutic strategy for heart failure patients.

10. Implications for Future Research

EAT has significant implications for cardiovascular research due to its role in inflammation and atherosclerosis. It secretes pro-inflammatory cytokines and adipokines that may contribute to heart disease, making it a potential target for new diagnostic and therapeutic strategies. Future research can explore its use as a non-invasive biomarker for cardiovascular risk assessment and its response to various treatments, such as lifestyle changes, exercise and pharmacological interventions, and bariatric surgery. Additionally, understanding the genetic and epigenetic factors influencing EAT accumulation could lead to novel approaches for preventing and managing cardiovascular and metabolic diseases.

Investigating the relationship between PAT characteristics and cardiovascular outcomes across diverse populations may help clarify its role as a biomarker or therapeutic target in cardiovascular disease. Such studies could pave the way for personalized approaches to managing

cardiovascular risk associated with PAT accumulation. In summary, a comprehensive approach that includes genetic, epigenetic, molecular, and clinical studies will be crucial for fully understanding the role of EAT and PAT in cardiovascular health. This will aid in developing effective strategies for early diagnosis, risk assessment, and personalized treatment of cardiovascular diseases.

Table 1. Comprehensive overview of EAT across various patient groups.

Reference	Clinical Population	EAT Quantification Imaging Modality	Key Findings
Heart Failure			
Obakata M et al. (2017)[37]	99 Obese HFpEF 96 Non-obese HFpEF 71 Controls	Echocardiography	• ↑EAT volume in obese HFpEF than non-obese HFpEF • ↑pericardial restraint (PCWP-RA) in HFpEF
Haykowsky MJ et al. (2018)[82]	100 Obese HFpEF 61 Controls	MRI	• ↓EAT in HFpEF and paradoxically associated with ↑ peak $VO_{2.}$
van Woerden G et al. (2018)[42]	64 HFpEF 20 Controls	MRI	• ↑EAT volume in HFpEF • ↑EAT associated with ↓LV GLS, ↓EF, ↑LA volume, ↑troponin, diabetes
Pugliese NR et al. (2021)[54]	188 HFpEF 205 HFrEF 44 Controls	Echocardiography	• ↑EAT thickness in HFpEF • ↓EAT thickness in HFrEF than HFpEF and controls. • In HFpEF, ↑EAT is inversely correlated with peak VO_2 and AVO_{2diff} • In HFrEF, ↓EAT associated with worse left ventricular systolic dysfunction (LVEF, LVGLS)
van Woerden G et al. 2021[83]	105 HFpEF	MRI	• ↑EAT is associated with adverse prognosis in HFpEF and HFmrEF • EAT associated with all cause mortality and HF hospitalization. • ↑EAT associated with ↓LV longitudinal strain and ↑pulmonary artery systolic pressure.
Gorter TM et al. 2020[43]	75 HFpEF	Echocardiography	• ↑EAT is associated with ↑BMI, ↑RVEDP, ↓$VO_{2max.}$ • EAT was not associated with LV filling pressure.
Tromp J et al. 2021[84]	47 HFpEF 204 HFrEF 113 Controls	MRI: EAT mass Echocardiography: EAT thickness	• ↑EAT mass in HFpEF compared to controls. • EAT/LVMass ratio and EAT thickness reduced in HFpEF and HFrEF • EAT mass negatively associated with LV strain in HFpEF

			• EAT mass positively associated with ECV in HFpEF
Zamani SK et al. 2023[44]	28 HFpEF	MRI	• ↑EAT associated with ↑LV eccentricity index. • PAT is strongly related to LV eccentricity index. • LV eccentricity is not related to BMI, subcutaneous fat, visceral fat, and pulmonary vascular resistance. • Dynamic exercise did not exacerbate cardio-mechanical interaction.
He Sh et al. 2022[85]	5 HFpEF 5 Non-HF	EAT biopsy	• EAT proteome strongly related to, lipid metabolic disorder, inflammation, and mitochondrial dysfunction
Koepp KE et al. 2020[4]	77 HFpEF with high EAT 92 HFpEF with lower EAT	Echocardiography	• ↑EAT associated with BMI, ↑LV eccentricity index, ↑RA pressure, ↑PA pressure, ↑PCWP, ↓VO_{2max}
Rao VN et al. 2021[86]	1350 with no HF 36 developed HF	CT	• ↑EAT associated with incident of HFpEF. • Pericardial fat associated with mortality.
Wu CK et al. 2017[87]	63 HFpEF 59 Controls	MRI	• EAT volume in HFpEF similar to Controls. • EAT associated with worse ECV
Wu CK et al. 2020[88]	163 HFpEF 34 HFrEF 108 Controls	MRI	• ↑EAT mass in HFpEF compared to HFrEF and controls. • ↑EAT is associated with LVEDV and LV mass, LA volume, and extracellular volume.
Jin X et al. 2022[89]	99 HFpEF 366 HFrEF/HFmrEF 140 Controls	Echocardiography	• ↑EAT in HFpEF compared to HFrEF/HFmrEF, and controls. • EAT associated with worse LA and LV function in HFpEF but better LA & LV function in HFrEF/HFmrEF.
Ardissino M et al. 2022[90]	42,598	MRI	• ↑EAT associated with ↑LV wall thickness, ↑LV mass, ↑concentric pattern of LV remodeling, ↓LVSVi, ↓LV function (↓LVGFI).
Venkateshvaran A et al. 2022[91]	182 HFpEF	Echocardiography	• ↑EAT group of HFpEF associated with higher BMI, lower NT-proBNP, higher LV septal wall thickness, inflammation,

			insulin resistance, dyslipidemia, endothelial dysfunction. • ↑EAT not associated with CFR.
Ying W et al. 2021[92]	55 HFpEF 33 Controls	MRI	• ↑EAT thickness in HFpEF • ↑EAT associated with lower global well-being score.
van Woerden G et al. 2021[7]	102 HFpEF	MRI	• EAT primarily surrounds RV. • EAT is associated with ↑RV mass. • ↑Atrial EAT in AFib patients compared to non-AFib.
Doesch Ch et al. 2010	66 Congestive Heart failure 32 Controls	MRI	• ↑EAT mass in CHF. • ↓EAT mass/LVMi ratio in CHF compared to controls.
Kenchaiah S et al. 2021[93]	6,402 with no HF 383 developed HF	CT	• PAT accumulation associated with incident of HFpEF and HFmrEF, but not HFrEF
Mahabadi AA et al. 2022	237 with no HF 142 developed HF	Echocardiography	• EAT is associated with the development of HFpEF
Lin J et al. 2021[94]	51 HFpEF 40 Controls	Echocardiography	• ↑EAT in HFpEF. • EAT associated with impaired LV longitudinal strain, ↑adipocyte fatty acid-binding protein, ↑risk of HF hospitalization.
van Woerden G et al. 2022[83]	50 HFpEFwith high EAT 52 HFpEF with lower EAT	MRI	• HFpEF with high EAT had ↑RVEDV, ↑RV mass, and impaired LA strain. • HFpEF with high EAT associated with HF hospitalization and mortality even after adjustments for BMI.
INOCA			
Khan I et al. (2023)[65]	125 INOCA 83 High EAT>125 mL 42 Low EAT<125 mL	CT	• ↑EAT volume more common in men and associated with ↑BMI, hypertension, ↑LVMi, and C-reactive protein.
Alam MS et al. (2013)[64]	137 INOCA	CT	• ↑EAT associated with impaired myocardial flow reserve.
Qi L et al. 2020[95]	72 INOCA 48 Controls	CT	• ↑EAT thickness and volume in INOCA • The presence of hypertension, triglyceride levels, EAT thickness and volume showed a significant association with INOCA.
Coronary Artery Calcification			

Kim BJ et al. 2015[96]	448 CACs >0 vs. 1,851 CACs =0	Echocardiography	• 8.3% prevalence of CAC in ↓EAT thickness quartile. 28.3% prevalence of CAC in the ↑EAT thickness quartile
Coronary Artery Disease			
Shambu SK et al. (2020)[97]	411 CAD patients vs. 92 normal coronaries	Echocardiography	• ↑EAT thickness in CAD
Hajsadeghi F et al. (2014)[98]	245 suspected CAD	CT	• EAT directly associated with CAD. • EAT predicts MACE independent of age and conventional risk factors.
Liu Z et al. 2019[99]	614 high cardiovascular disease risk	CT	• ↑EAT attenuation associated with higher risk of CAD including age, sex, BMI, total cholesterol, neutrophil to lymphocyte ratios, CAC score.
Zhou J et al. 2019[100]	5,743 Derivation cohort 2,844 external validation cohort	CT	• ↑EAT volume was observed in patients with CAD. • Addition of EAT measurement to conventional risk factors, improved the prediction of obstructive CAD.
Jehn S et al. 2023[101]	657 acute chest pain	Echocardiography	• EAT strongly and independently predicts the presence of obstructive CAD in patients presenting with acute chest pain.
Diabetes Mellitus			
Wang CP et al. (2009)[102]	49 T2DM 78 nondiabetic controls	CT	• ↑EAT volume in T2DM. • EAT volume associated with CACs.
Fatty Liver			•
Psychari SN et al. (2015)[103]	57 Nonalcoholic Fatty Liver 48 age-matched controls	Echocardiography	• EAT thickness ↔ • ↔ between EAT thickness and cardiac structure and function
COVID19			
Conte C et al. (2021)[104]	192 COVID19	CT	• ↑EAT attenuation, a marker of EAT inflammation predicts COVID-19, but not EAT volume or obesity. • Positive correlation between EAT attenuation and Troponin T •
Slipczuk L et al. (2021)[105]	493 COVID19 296 Alive	CT	• ↑EAT volume & ↑CACs in dead cohort

	197 Dead		
Iacobellis G et al. 2020	41 COVID19	CT	• ↑EAT attenuation with severe and critical COVID19. • EAT attenuation was similar to that observed in CAD between different stages of the COVID19, despite the COVID19 patients having the history of CAD.
HIV			
Brener M et al. (2014)[106]	579 HIV-infected 353 HIV-uninfected	CT	• ↑EAT volume in HIV-infected
AFib			
Hasebe H et al. (2020)[107]	50 PAF 50 CAD 50 Controls	CT	• ↑EAT volume in PAF and CAD
Kenchaiah S et al. (2021)[93]	6,785 without pre-existing CVD 2,130 Normal peri fat volume 1,462 high peri fat volume	CT	• ↓EAT volume in women than men. • ↑EAT volume augmented the risk of HFpEF than HFrEF (15 yrs follow-up) • ↑EAT volume was associated with higher risk of HF in women.

EAT: epicardial adipose tissue; CACs: coronary artery calcium score; T2DM: type 2 diabetes mellitus; PAF: paroxysmal atrial fibrillation; CAD: coronary artery disease; LVRR: left ventricular reverse remodeling; LVGFI: left ventricular global function index; LVSVi: left ventricular stroke volume index; LVMi: left ventricular mass index; CFR: coronary flow reserve; MACE: major adverse cardiovascular events.

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Chapter 5

Dissertation Summary and Concluding Remarks

Pericardial fat, which includes both epicardial adipose tissue (EAT) and paracardial adipose tissue (PAT), holds significant importance in cardiovascular research due to its metabolic activity and proximity to the heart.[1] This fat is not merely a passive anatomical structure but an active contributor to cardiovascular pathophysiology.[2] As such, studying these fat depots is crucial for understanding their influence on various aspects of cardiovascular health, including their potential role in the development and progression of heart disease.[3] By examining the metabolic characteristics of EAT and PAT, valuable insight can be gained into how these fat deposits contribute to cardiovascular risk and devise targeted interventions to mitigate their harmful effects.[4]

In Chapter 3, we presented novel findings on the impact of EAT on both coronary vascular function and cardiac structure and function among women experiencing suspected ischemia but without obstructive coronary artery disease (INOCA). The assessment of EAT area was derived from a single high-resolution steady-state free precession cine image in the horizontal long-axis imaging plane, validated against three-dimensional cardiac computed tomography within our research group. Coronary vascular function was evaluated by gold-standard coronary angiography with vasoactive provocation testing and core lab adjudication. Post-hoc power analyses using G*Power 3.1.4 indicated that with our study N of 294, our range of effect sizes (0.05-0.3) yielded a range of statistical power of 0.10 to 0.99, based on two-tailed alpha of 0.05. Notably, the data do not support a relationship between EAT and coronary vascular dysfunction but suggests that EAT may play an important role in the development of concentric remodeling and diastolic dysfunction in women with suspected INOCA. Chapter 4 examined the relationship between EAT and PAT and cardio-mechanical interaction in patients with heart failure and

preserved ejection fraction (HFpEF) using cardiac magnetic resonance imaging (MRI) both at rest and during dynamic exercise. Post-hoc power analyses indicated that with our study N of 28, our range of effect sizes (2.37 – 3.15) yielded a range of statistical power of 0.99 to 1.0, based on two-tailed alpha of 0.05. The findings indicate that excessive EAT and PAT significantly contribute to adverse cardio-mechanical interaction in obese HFpEF patients. Further work is needed to understand to contribution of, and interaction with, exercise, which was limited in this investigation by the supine body position and low exercise intensity chosen. Taken together, the collection of work presented herein emphasizes the importance of a comprehensive study of pericardial fat, including EAT and PAT, as crucial for unraveling their intricate roles in cardiovascular diseases. This work not only enhances our understanding of pericardial fat impact but also paves the way for developing targeted interventions aimed at improving cardiac health and function.

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