Research paper

Pericardial fat volume is related to endothelial-mediated coronary blood flow in women with suspected coronary microvascular dysfunction. A report from the Women's Ischemia Syndrome Evaluation-Coronary Vascular Dysfunction (WISE-CVD) study

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ABSTRACT

Background: Coronary microvascular dysfunction is prevalent in women with signs and symptoms of ischemia but no obstructive coronary artery disease (CAD) and is associated with an adverse prognosis. Elevated pericardial fat volume predicts adverse cardiac events, but mechanistic pathways of the association are not well understood.
Methods: 118 women enrolled in the NHLBI-sponsored Women's Ischemia Syndrome Evaluation-Coronary Vascular Dysfunction study with suspected coronary microvascular dysfunction but no obstructive CAD underwent adenosine stress 1.5 T cardiovascular magnetic resonance imaging (CMR) imaging and invasive coronary reactivity testing. Semi-quantitative myocardial perfusion reserve index (MPR) index was derived from perfusion images. Pericardial fat volume was measured by manually contouring the cardiac margins and adjacent adipose tissue on a single trans-axial HASTE slice at the level of the left main coronary artery origin and indexed to body surface-area. Simple standard deviation analysis obtained for continuous variables and frequency (percent) for categorical variables. The relationships between pericardial fat volume and coronary reactivity testing parameters were examined by correlation and multivariable regression analyses.
Results: Women with suspected coronary microvascular dysfunction had a mean age of 55 ± 10 years, body mass index (BMI) of 28 ± 7 kg/m^2, 44 % had a history of smoking, 63 % hypertension, 8 % diabetes, and 20 % dyslipidemia. CMR imaging-derived pericardial fat volume and coronary blood flow response to intracoronary acetylcholine (Δ CBF) were negatively correlated ($r = -0.32$, $p = 0.0013$). After adjustment for age, number of risk factors, high-density lipoprotein (HDL), and cold pressor diameter response, pericardial fat volume remained a significant predictor of Δ coronary blood flow ($p = 0.04$). There was no association with other coronary reactivity testing measures or CMRI derived MPR index.
Conclusions: Among women with suspected coronary microvascular dysfunction but no obstructive CAD, pericardial fat volume appears to be related in a hypothesized adverse direction to coronary microvascular endothelial function. These results support further work confirming and extending these results to investigate pericardial fat volume as mechanistic pathway and potential treatment target for coronary microvascular dysfunction-related adverse events.
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1. Background

Women with signs and symptoms of cardiac ischemia but no obstructive CAD pose a diagnostic and therapeutic challenge. Evidence from the Women's Ischemia Syndrome Evaluation study has demonstrated that almost half of these women have coronary microvascular dysfunction [1], and at higher risk for major adverse cardiovascular events (MACE) including non-fatal myocardial infarction, stroke, heart failure with preserved ejection fraction, and even death [2–4]. Invasive coronary reactivity testing using intracoronary infusions of vasoactive substances is the gold standard method in diagnosing different pathways contributing to coronary microvascular dysfunction, although it is not readily available in the community [5]. Recently, non-invasive imaging such as cardiac positron emission tomography (PET) [6], and cardiovascular magnetic resonance (CMR) imaging has emerged as a useful diagnostic tool to predict coronary microvascular dysfunction, yet their use is still limited in diagnosing specific pathways contributing to coronary microvascular dysfunction [7].

Pericardial fat volume assessed by non-contrast cardiac computed tomography (CT) has been associated with several medical conditions including, metabolic syndrome, coronary artery calcification, atherosclerotic coronary artery disease, myocardial ischemia, and adverse cardiac outcomes [8–11], but has not been fully investigated in women with suspected coronary microvascular dysfunction. Further, the pathophysiological mechanisms relating pericardial fat volume to adverse coronary vascular disease events is not well understood. Pericardial fat volume assessment is feasible using CMR imaging, in addition to CT and echocardiography [12]. The aim of this study is to evaluate the relationship between pericardial fat volume and coronary microvascular dysfunction using invasive coronary reactivity testing and non-invasive CMR imaging in women enrolled in the National Heart, Lung and Blood Institute (NHLBI)–sponsored Women's Ischemia Syndrome Evaluation – Coronary Vascular Dysfunction study.

2. Methods

2.1. Study population

The total of 437 women with signs and symptoms of ischemia and no obstructive coronary artery disease were enrolled in the NHLBI-sponsored Women's Ischemia Syndrome Evaluation-Coronary Vascular Dysfunction study using prior inclusion and exclusion criteria [7]. Following exclusion of 63 subjects due to self-withdrawal or contraindications to CMR, 374 women completed a baseline CMR, among which 279 underwent clinically indicated coronary reactivity testing, and 206 with available images were included in pericardial fat volume estimation resulting in a total of 118 women with complete coronary reactivity, CMR perfusion imaging and CMR-derived pericardial fat volume estimation data for the current analysis (Fig. 1).

Women with obstructive CAD ($\geq$50 % in one or more epicardial coronary artery), acute coronary syndrome, severe valvular heart disease, cardiogenic shock, acute myocardial infarction (MI), contraindication to CMR imaging, chest pain due to non-ischemic etiology, prior non-cardiac illness with estimated life expectancy <4 years, severe renal impairment, significant pulmonary disease, inability to give an informed consent were excluded from the study. All women underwent
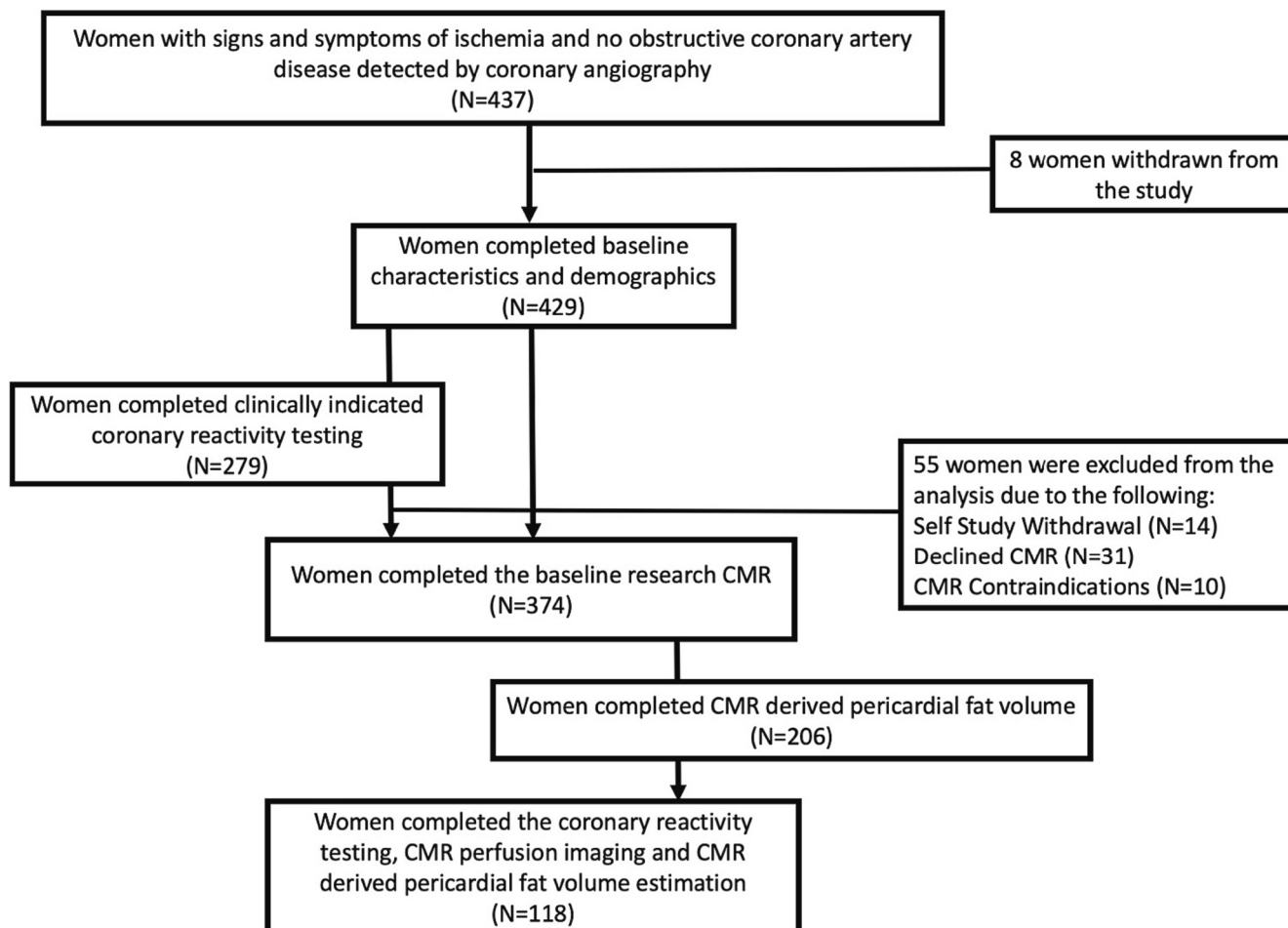

Fig. 1. Study population with actual numbers of women enrolled in the Women's Ischemia Syndrome Evaluation Study-Coronary Vascular Dysfunction.

clinically indicated coronary reactivity testing and CMR imaging. Institutional review boards at each of two sites of enrollment approved the protocol, written informed consent was obtained from each participant, and data were monitored by an independent data safety monitoring committee (IRB No: Pro00014906/Ame00016240). Demographic, baseline characteristics including weight, height, body mass index (BMI), heart rate, blood pressure, cardiovascular risk factors, and medications were documented at each site (Cedars-Sinai Medical Center and University of Florida Medical Center) using standardized questionnaires as previously published [7].

2.2. Coronary reactivity testing protocol

Coronary reactivity testing was performed as previously published [5]. In brief, using a Doppler flow wire (FloWire® Volcano) positioned in the proximal left anterior descending artery. Intracoronary vasoactive substances were given sequentially to measure coronary microvascular endothelial dependent and non-endothelial dependent function (Table 2), as previously published [5,13]. In particular endothelial-dependent coronary microvascular function was determined by Doppler measurement during intra-coronary infusion of acetylcholine. Normal endothelial-dependent microvascular response was defined as a coronary blood flow increase >50 % at the highest dose of acetylcholine. Change in coronary blood flow (ΔCBF) to acetylcholine was calculated from the Doppler-derived time velocity integral and vessel diameter by the following equation: Coronary blood flow = π (average peak velocity/ 2)(vessel diameter/2)2. Vessel diameter was calculated 5 mm distal to the Doppler wire.

2.3. Cardiovascular magnetic resonance imaging protocol

Participants underwent standardized adenosine stress/rest CMR imaging with electrocardiogram gating and a phased array coil protocol (1.5 T Magnetom Avanto; Siemens Healthcare, Erlangen, Germany) as previously published [14,15].

2.3.1. Myocardial Perfusion Reserve (MPR) index assessment

First-pass contrast perfusion imaging was performed using gadolinium contrast of 0.05 mmol/L/kg (Gadodiamide; Omniscan, Amersham, Piscataway, NJ) infused at 4 mL/s, followed by 20 mL saline at 4 mL/s. Vasodilator stress was adenosine 140 μg/kg/min infused for 2 min into the arm contralateral to the contrast injection, prior to first-pass perfusion imaging, and continued until completion of the perfusion imaging data acquisition. Resting first-pass perfusion CMR imaging was acquired 10 min later [7]. MPR index was measured as a ratio of the relative up slopes rest/stress normalized to LV cavity blood pool relative up slopes using CAAS MRV 3.3 software (Pie Medical Imaging, Netherlands), as previously described [7].

LV mass was assessed by manually tracing the epicardial and endocardial borders of short-axis cine images [7].

2.3.2. Pericardial fat volume measurement

The adipose tissue volume surrounding the heart can be divided into two compartments- the adipose tissue volume enclosed by the visceral pericardium, also known as epicardial adipose tissue volume and the adipose tissue volume outside the pericardium within the chest wall at the level of the heart. Compared to non-contrast CT, CMR imaging allows poor visual identification of the visceral pericardium, which is the demarcation between the adipose tissue volume enclosed by the pericardium called the epicardial adipose tissue volume, and the adipose tissue volume outside the pericardium at the level of the chest wall, known as the cardiac adipose tissue volume, therefore, we included both epicardial adipose tissue and extra-pericardial intrathoracic adipose tissue volume under total pericardial fat volume. Pericardial fat volume was measured using a single trans-axial Half Fourier Single-shot Turbo Spin-Echo (HASTE) slice at the level of the left main coronary artery

origin [16]. Contours were drawn manually, and care was taken to include cardiac margins and adjacent adipose tissue. Pericardial fat volume measurements were quantified semi-automatically using Object System Research Visual Pro post-processing software [16] by an experienced reader blinded to patient's clinical data. Pericardial fat volume was indexed to body surface-area, as previously published [16] (Fig. 2).

Of note the semantics of these definitions have changed over time but for the purposes of this discussion we will use the aforementioned terms. Prior work using non-contrast cardiac CT demonstrated an excellent correlation between total epicardial adipose tissue around the heart and the epicardial adipose tissue at the level of the left main coronary artery [17]. In addition, prior work using non-contrast cardiac CT has shown a high correlation between epicardial adipose tissue and extra-pericardial adipose tissue [8,10].

2.3.3. Statistical analysis

Variables were summarized using basic mean ± standard deviation for continuous variables and frequency (percent) for categorical variables. Bivariate Pearson correlation was used to evaluate the degree of linear associations between pericardial fat volume and continuous variables among patient demographics, baseline variables, and coronary reactivity testing parameters. Multiple linear regression was used with coronary blood flow as the outcome to evaluate the relationship of coronary blood flow and pericardial fat volume, adjusting for other variables (the model reported here used left ventricular mass and low density lipoprotein (LDL)). Model fit was assessed through the analysis of residuals. Statistical significance for hypothesis testing was set at the 0.05 level. All analyses were done using SAS version 9.3 (SAS Institute, Cary, NC).

3. Results

3.1. Participants baseline information and coronary reactivity testing results

Participants' baseline characteristics are summarized in Table 1 and demonstrated on average mid-life women with an elevated mean BMI, and high prevalence of hypertension. There were 27 participants with one or more pathway testing missing data due to technical challenges and difficulties during the procedure.

3.2. Pericardial fat volume and baseline characteristics

Pericardial fat volume inversely correlated with HDL cholesterol ($r = -0.25$, $p = 0.015$), and positively with age ($r = 0.36$, $p < 0.0001$), glucose level ($r = 0.28$, $p = 0.0031$), and number of cardiac risk factors (number of the following conditions were summed for each person: hypertension, hyperlipidemia, diabetes mellitus, history of smoking, family history of CAD; $r = 0.36$, $p \leq 0.001$). There was no correlation between pericardial fat volume and any of the following individual variables: LDL, triglycerides, creatinine, hemoglobin, or brain natriuretic peptide.

3.3. Pericardial fat volume and coronary reactivity testing variables

ΔCBF inversely correlated with pericardial fat volume Table 2. There were no other correlations with the other invasive measures of coronary microvascular dysfunction Table 2. Pericardial fat volume did not correlate with the non-invasive MPR index obtained from CMR ($r = -0.06$, $p = 0.44$).

3.3.1. Multivariable analysis

To further explore the association between Δ CBF and pericardial fat volume, linear regression modeling was performed for ΔCBF as the outcome. Analysis showed that when adjusting for LDL cholesterol, left ventricular mass, pericardial fat volume remained significantly
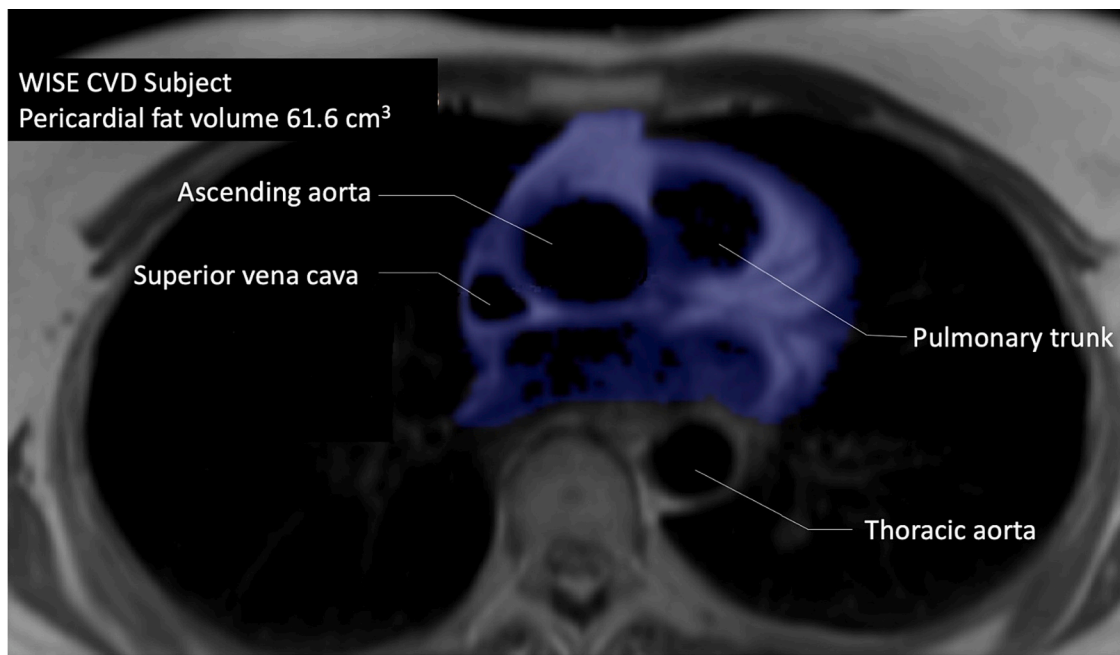
Fig. 2. Pericardial adipose tissue shown in a blue overlay over cardiac magnetic resonance image (slice closest to the left main coronary artery) in a Women's Ischemia Syndrome Evaluation – Coronary Vascular Dysfunction participant.

Table 1

Baseline characteristics, comorbidities, laboratory findings, medications and CFT parameters ($n = 118$ women).

Variable	Mean ± SD (range) or %
Age	54 ± 11 years (26, 74)
Hyperlipidemia	11
Hypertension	32
Diabetes mellitus	8
Smoking	46
BMI (kg/m^2)	29 ± 7 (18, 55)
Total cholesterol (mg/dL)	177 ± 41 (99, 301)
LDL (mg/dL)	101 ± 34 (32, 194)
HDL (mg/dL)	57 ± 16 (23,103)
Triglycerides (mg/dL)	82 ± 43 (24, 254)
Fasting blood glucose (mg/dL)	86 ± 10 (61, 190)
BNP (mg/dL)	106 ± 167 (9, 1406)
Statin therapy (%)	45
Insulin therapy (%)	1
Oral diabetes therapy (%)	5
CFR	2.82 ± 0.72 (1.7, 5.5)
CBF	93.85 ± 100.41 (−47.67, 459)
ACH response	−0.12 ± 14.35 (−49.72, 31.98)
NTG response	16.5 ± 13.31 (−14.62, 50.33)
COP response	4.16 ± 12.36 (−20.09, 44.86)

ACH = acetylcholine, BMI = body mass index, BNP = brain natriuretic peptide, CBF = coronary blood flow, CFR = coronary flow reserve, COP = cold pressor, HDL = high density lipoprotein, LDL = low density lipoprotein, NTG = nitroglycerin.

associated with ΔCBF, with the model accounting for 20 % of the variance of ΔCBF (r^2 = 0.2) (Table 3).

4. Discussion

To the best of our knowledge, this is the first study to show that pericardial fat volume is related to coronary microvascular endothelial function. These data, in the hypothesized adverse direction, support the potential role of pericardial fat volume as a mechanistic pathway to cardiac events. Specifically, our results in women without obstructive CAD, suggest a mechanism of microvascular dysfunction-related myocardial ischemia as the link between pericardial fat volume and

Table 2

Pearson correlation of pericardial fat volume and invasive coronary microvascular dysfunction parameters ($n = 118$ women).

Coronary microvascular dysfunction variables	Vasoactive IC infusion	Pathway	Correlation coefficient	*p* value
Coronary flow reserve	Adenosine	Non-endothelial dependent microvascular	0.04	0.65
Change in coronary blood flow	Acetylcholine	Endothelial-dependent microvascular	−0.32	**0.0013**
Coronary diameter response	Acetylcholine	Endothelial-dependent macrovascular	0.03	0.71
Coronary diameter response	None[a]	Endothelial-dependent	0.15	0.12
Coronary diameter response	Nitroglycerin	Non-endothelial dependent macrovascular	0.004	0.97

[a] Cold pressor test, ice pack placed on left arm ($N = 55$) or forehead ($N = 51$).

Table 3

Multivariable regression modeling for prediction of change in coronary blood flow in response to acetylcholine ($N = 77$).

	Parameter estimate	Standard Error	*P*-value
Pericardial fat volume	−4.99	1.9	0.01
LV mass	−1.88	0.8	0.02
LDL	0.48	0.3	0.13

LV = left ventricle, LDL = low density lipoprotein.

adverse cardiac events.

Our finding extends a previous study demonstrating CT-derived periventricular epicardial adipose tissue volume inversely related to coronary endothelial function, keeping in mind that transthoracic Doppler echocardiographic derived CFR is a measure of non-endothelial dependent microvascular function [18]. We did not find an association

between pericardial fat volume and other microvascular coronary artery variables. Furthermore, we also did not find correlation between pericardial fat volume and change in CMR imaging-derived MPR index measurement of perfusion. This finding is also consistent with previous work published by Nakanishi K et al., which demonstrated no correlation between multi-detector computed tomography (MDCT)-derived total epicardial adipose tissue volume and transthoracic Doppler echocardiographic- derived CFR [18].

Among women with signs and symptoms of ischemia, but no obstructive CAD, coronary microvascular dysfunction carries an elevated risk for MACE [2,4,19–21]. Prior work demonstrated that CMR imaging can be useful for the noninvasive detection of coronary microvascular dysfunction [7], and that pericardial fat volume can be measured from standard CMR imaging scans [16]. Other evidence has demonstrated a significant association between epicardial adipose tissue measured by CT, an easily obtained and reproducible imaging biomarker, with myocardial ischemia and MACE [11]. Our current findings linking pericardial fat volume with coronary microvascular dysfunction suggests that this relationship may also be true using CMR imaging in women with no obstructive CAD and suspected coronary microvascular dysfunction.

Traditionally, adipose tissue has been viewed as an energy storage tissue that regulates thermogenesis and gluconeogenesis, however it also produces several bioactive substances [22,23] including inflammatory mediators [24,25], proposing the hypothesis that pericardial adipose tissue may contribute to the development of endothelial dysfunction and coronary atherosclerosis through a local production of inflammatory cytokines [26,27]. This hypothesis is supported by work with animal models which demonstrated that increase in peri-coronary adipose tissue exacerbated coronary endothelial dysfunction [28]. Epicardial adipose tissue which is the adipose tissue surrounding the coronary vessels may also play a role in developing atherosclerosis and adverse cardiovascular outcomes [29].

Adipokines such as resistin and leptin secreted from adipose tissue exert predominantly pro-inflammatory effects, whereas adiponectin is classically anti-inflammatory and therefore, adipocytes can be viewed components of the immune system [23,29]. Leptin is expressed on most immune cells and promotes their activation [29]. Recently, it has been shown that epicardial adipose tissue-derived leptin selectively impairs coronary endothelial dependent dilation in Ossabaw swine animal models with metabolic syndrome [29].

Furthermore, in studies of obese patients compared to lean controls, (both without evidence of obstructive CAD), the obese patients had more evidence of coronary microvascular dysfunction, which was associated with increased levels of the inflammatory markers interleukin-6 (IL-6) and tumor necrosis factor alpha [30]. Although our study didn't examine any inflammatory effect, our prior work in women with suspected coronary microvascular dysfunction showed an association with inflammatory biomarkers and endothelial dysfunction [31,32].

Combined with the evidence provided in previous studies, our current results suggest that the inflammatory effect mediated by pericardial fat may predominantly impact the coronary microvasculature and result in coronary endothelial dysfunction. Further studies needed to explore this correlation including peri-coronary fat measures and inflammatory biomarkers such as leptin levels and their effect on ischemia and potential development of atherosclerosis.

4.1. Limitations

Only women were examined in our cohort therefore results can't be generalized. Compared to CT, the separation of epicardial and extra-pericardial fat is less distinct with CMR imaging suggesting that whole heart pericardial fat volume (should) be measured, and therefore the two components were not studied separately despite evidence that epicardial fat appears to be a better cardiovascular risk biomarker [10,11]. Although studies have shown high correlations between whole

heart pericardial fat volume and pericardial fat volume at the level of the left main coronary artery [16,17,33], it is noteworthy that coronary microvascular dysfunction is global dysfunction of the microvasculature, suggesting that whole heart pericardial fat volume be measured; however this is a time-consuming task.

5. Conclusions

Among women with suspected coronary microvascular dysfunction but no obstructive CAD, pericardial fat volume appears to be related in a hypothesized adverse direction to microvascular coronary endothelial function. These results support further work confirming and extending these results to investigate pericardial fat volume as mechanistic pathway and potential treatment target for coronary microvascular dysfunction-related adverse events.

Abbreviations

CAD	Coronary Artery Disease
CMR	Cardiovascular Magnetic Resonance
MPR	Myocardial Perfusion Reserve
HASTE	Half Fourier Single-shot Turbo Spin-Echo
BMI	body mass index
ΔCBF	change in coronary blood flow
HDL	high density lipoprotein
MACE	major adverse cardiovascular events
PET	positron emission tomography
CT	computed topography
MI	myocardial infarction
LDL	low density lipoprotein
MDCT	multi-detector computed tomography
CFR	coronary flow reserve

Ethics approval and consent to participate

This study was approved by the Cedars-Sinai Medical Center and University of Florida institutional review boards, and written informed consent was obtained for all participants.

Consent for publication

Not applicable.

Ethical statement

All authors ensure that the work described has been carried out in accordance with The Code of Ethics of the World Medical Association and the manuscript is in line with the Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals.

CRediT authorship contribution statement

Sofy Landes: Conceptualization, Data curation, Formal analysis, Writing – original draft, Writing – review & editing. **Haider Aldiwani:** Conceptualization, Data curation, Formal analysis, Writing – original draft, Writing – review & editing. **Louise Thomson:** Data curation, Formal analysis, Investigation, Resources, Writing – review & editing. **Janet Wei:** Data curation, Formal analysis, Investigation, Methodology, Resources, Writing – review & editing. **Ahmed Al-Badri:** Data curation, Formal analysis, Investigation, Methodology, Project administration, Writing – review & editing. **Puja K. Mehta:** Data curation, Formal analysis, Investigation, Methodology, Writing – review & editing. **Michael Pedram:** Data curation, Formal analysis, Investigation, Methodology, Resources, Writing – review & editing. **Manish Motwani:** Data curation, Formal analysis, Investigation, Methodology, Writing – review & editing. **Galen Cook-Weins:** Data curation, Formal analysis, Investigation, Methodology, Writing – review & editing. **George Sopko:** Data curation, Formal analysis, Investigation, Methodology, Writing – review & editing. **Carl J. Pepine:** Data curation, Formal analysis, Investigation, Methodology, Resources, Writing – review & editing. **C. Noel Bairey Merz:** Data curation, Formal analysis, Funding acquisition, Investigation, Project administration, Resources, Supervision, Writing – review & editing. **Damini Dey:** Data curation, Formal analysis, Investigation, Project administration, Supervision, Validation, Writing – review & editing.

Declaration of competing interest

Dr. Bairey Merz has received honorarium from Abbott Diagnostics and serves on the Board of Directors for iRhythm. All other authors declare no competing non-financial interests.

Data availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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