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ORIGINAL RESEARCH

Epicardial Fat Tissue: A Potential Marker for Coronary Microvascular Dysfunction

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BACKGROUND: Coronary microvascular dysfunction (CMD), which mimics symptoms of obstructive coronary artery disease, has significant prognostic implications. While epicardial adipose tissue normally has a protective role, increased epicardial adipose tissue is associated with inflammation and may contribute to CMD. However, a direct correlation remains unclear. We aimed to investigate this association.

METHODS AND RESULTS: The CMDR (Coronary Microvascular Disease Registry) is a prospective, 2-center registry that is enrolling patients with angina and nonobstructive coronary artery disease who underwent invasive hemodynamic assessment of the coronary microvasculature. Patients with chest computed tomography within 1 year of CMD evaluation were included. We measured epicardial fat volume (EFV) and calculated the EFV index. Logistic regression analysis was used to investigate the association between EFV and EFV index to CMD. Our study included 130 CMDR patients with associated chest CT; 35 were diagnosed with CMD. The CMD-negative patients were younger than the CMD-positive patients (58.52±11.97 versus 63.37±9.56 years; P=0.033), with numerically fewer women (64.2% versus 74.3%; P=0.279). Univariate regression analysis demonstrated a statistically significant association between EFV index and CMD diagnosis (odds ratio, 1.037 [95% CI, 1.014–1.063]; P=0.003), while no significance was observed for EFV (odds ratio, 1.006 [95% CI, 0.995–1.017]; P=0.292).

CONCLUSIONS: Our results suggest a strong association between EFV index (a significant risk factor) and the presence of CMD. Future studies involving larger cohorts are needed to confirm the association of epicardial adipose tissue with CMD and investigate therapeutic targets to prevent CMD.

REGISTRATION: URL: https://www.clinicaltrials.gov; unique identifier: NCT05960474.

Key Words: computed tomography ■ coronary artery disease ■ coronary microvascular dysfunction ■ epicardial fat

It is now known that epicardial coronary artery disease (CAD) is not the only pathologic entity in ischemic heart disease and that the role of microcirculation has been underestimated for years. Coronary microvascular dysfunction (CMD) refers to a range of structural and functional abnormalities within the coronary microcirculation, leading to impaired coronary blood flow that results in myocardial ischemia.[1] CMD is often suspected in patients with typical chest pain or abnormal stress test results indicative of ischemia but with normal coronary arteries on angiography. In fact, >20% of patients undergoing cardiac catheterization for angina with no evidence of CAD on angiography have CMD.[2,3]

Epicardial adipose tissue (EAT) is visceral fat localized between the myocardium and the visceral layer of pericardium directly surrounding the coronary arteries and getting its blood supply from their branches.[4,5] EAT

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CLINICAL PERSPECTIVE

What Is New?

- Our study demonstrates that epicardial fat volume indexed to body surface area is an independent predictor of coronary microvascular dysfunction, while total epicardial fat volume is not.

What Are the Clinical Implications?

- The epicardial fat volume index may be a useful marker for identifying individuals at increased risk for coronary microvascular dysfunction, prompting earlier intervention and potentially improving outcomes.

Nonstandard Abbreviations and Acronyms

CMD	coronary microvascular dysfunction
CMDR	Coronary Microvascular Disease Registry
EAT	epicardial adipose tissue
EFV	epicardial fat volume
EFVi	epicardial fat volume index

has a protective function in normal conditions: providing the myocardium with free fatty acids and functioning as a buffer, protecting the heart from excess fatty acid[6]; however, increased EAT has been linked to many cardiovascular diseases including obstructive CAD, heart failure, and atrial fibrillation.[7–9] EAT can be measured quantitatively by using computed tomography (CT) or cardiac magnetic resonance imaging, which is reported as a precise volumetric measurement, epicardial fat volume (EFV).[10,11] Both contrast-enhanced and non–contrast-enhanced CT are used for EFV quantification.[11]

Despite extensive data demonstrating the association between obstructive CAD and EAT, limited research exists on the relationship between EAT properties and patients with CMD. Prior studies investigating CMD often relied on less precise noninvasive diagnostic methods,[12] while recent advancements in interventional cardiology offer a more comprehensive invasive hemodynamic assessment using coronary flow reserve and the index of microcirculatory resistance, leading to improved diagnostic capabilities for CMD.[13,14] Studies analyzing the relationship between EAT and CMD are currently lacking. Our present study aims to address this gap by investigating the relationship between EAT measured by CT and CMD measured by invasive hemodynamic techniques.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study Population

The CMDR (Coronary Microvascular Disease Registry) is a nationwide, prospective, multicenter registry that enrolls patients (both inpatient and outpatient) who undergo a comprehensive invasive hemodynamic assessment of the entire coronary arterial vasculature. At the time of this analysis, the CMDR had 2 active sites that contributed data to this ongoing registry.

Details of the CMDR and technique to assess microvasculature physiology via the Coroventis CoroFlow Cardiovascular System (Abbott Laboratories, Chicago, IL) were previously published.[13,15] In CMDR, the microvasculature is assessed invasively using the Pressure X physiology wire (Abbott Laboratories) using bolus thermodilution assessment to derive a coronary flow reserve and index of microcirculatory resistance. Acetylcholine provocative testing to evaluate coronary vasospasm was not protocolized and was performed at the discretion of the operator. Acetylcholine provocative testing results were not included in the present analysis.

This analysis presents results from patients enrolled in the CMDR from August 2021 to December 2023 at 2 MedStar Health centers (MedStar Washington Hospital Center, Washington, DC; and MedStar Southern Maryland Hospital Center, Clinton, MD). The CMDR includes patients with angina and nonobstructive CAD and ischemia with nonobstructive CAD. The CMDR collects baseline characteristics, comorbidities, medications, chest pain severity, noninvasive cardiovascular testing, coronary anatomy based on angiography, and physiologic measurements. The MedStar Washington Hospital Center institutional review board approved the study protocol, and all participants provided written informed consent

Epicardial Fat Quantification

For the current analysis, we selected patients in the CMDR who also underwent a chest or cardiac CT within 1 year of their invasive hemodynamic assessments for CMD. CT data sets were transferred to an imaging workstation for image analysis. EAT was defined as fat tissue located between the myocardium and visceral layer of the pericardium. Following established methods,[16] EFV was measured using commercially available software (syngo.via 8.6, Siemens Healthineers AG, Forchheim, Germany). The EAT was outlined by manually contouring the targeted area between the bifurcation of the main pulmonary artery (cranial border) and the last visible border of the pericardium (caudal border). Slices were

manually edited when the region of interest extended outside the pericardium. A 3-dimensional volume of interest was subsequently computed by interpolation. As suggested in previous literature, attenuation thresholds of –190 and –30 Hounsfield units were applied within the segmented area to identify voxels containing fat (Figure 1).[17,18] Total EFV (in cubic centimeters) were documented. Indexed EFV (EFVi) was calculated by dividing the measured EFV for each patient by the patient's body surface area. The observer assessing the EFV was blinded to the patients' baseline CMD data to minimize potential bias. Interobserver variability was calculated for 10 randomly selected patients who were remeasured by a second observer who was blinded to previous results.

Statistical Analysis

Categorical variables, reported as count and percentage, were compared using the χ^2 test or Fisher's exact test. Continuous data are presented as sample mean±sample SD and were compared using the *t* test or Wilcoxon rank-sum test, as appropriate. Statistical significance was declared at $P<0.05$. Univariate logistic regression analysis was performed to model the probability of being CMD-positive given EFV and EFVi, respectively. Linear regression was performed to model the correlation between EFVi and age. Statistical analyses were performed using SAS 9.4 (SAS Institute, Cary, NC) and R (Comprehensive R Archive Network version 4.1.3; R Project for Statistical Computing, Vienna, Austria).

RESULTS

Baseline Characteristics, EFV, and EFVi Measures

Our study included 130 patients, 73% (95/130) classified as CMD negative and 27% (35/130) as CMD positive. Table 1 displays the patients' baseline characteristics and clinical presentation. Compared with CMD-positive patients, those in the CMD-negative group were significantly younger (58.52±11.97 years versus 63.37±9.56 years; $P=0.033$) and had a higher average body mass index (32.87±7.02 kg/m^2 versus 29.36±6.26 kg/m^2; $P=0.005$) and a higher average body surface area (2.02±0.25 m^2 versus 1.9±0.25 m^2; $P<0.001$). Although the CMD-negative group contained fewer women, this difference was not statistically significant (64.2% versus 74.3%; $P=0.279$). There were also no significant differences between the 2 groups with respect to hypertension, hyperlipidemia, and diabetes. Moreover, no difference between the 2 groups was present in limiting symptoms with a Canadian Cardiovascular Society Angina score of 3 or 4 (30% versus 33.3%; $P=0.782$). Medications administered to both groups before the procedure are listed in Table 1, revealing a trend toward increased usage of high-intensity (40% versus 31.4%; $P=0.371$) and moderate-intensity statins in CMD-negative patients (28.4% versus 14.3%; $P=0.097$). EFV did not differ significantly between the 2 groups; however, EFVi was significantly

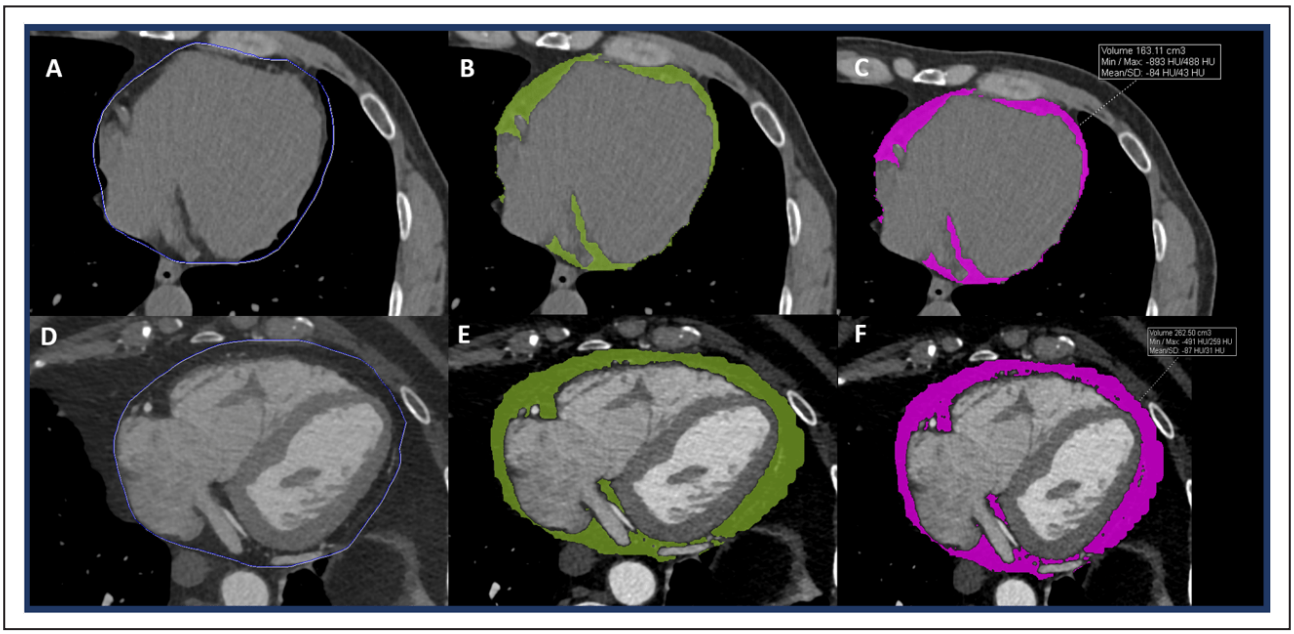

Figure 1. CT imaging of EFV measurement.
Quantification of EFV on nongated noncontrast (**A** through **C**) and gated coronary CT angiography (**D** through **F**) using semiautomated software. CT images with the epicardial boundary delineated by the blue contour line on each slice from bifurcation of the main pulmonary artery and the last visible border of the pericardium (**A** and **D**). Within the region of interest, fat voxels were identified using a threshold attenuation range of –190 to –30 Hounsfield units (**B** and **E**). The EFV is automatically calculated by the software (**C** and **F**). CT indicates computed tomography; and EFV, epicardial fat volume.

Table 1. Baseline Clinical Characteristics

Variable	Overall (N=130)	CMD negative (N=95)	CMD positive (N=35)	*P* value
Age, y	59.82±11.54	58.52±11.97	63.37±9.56	0.033
Body mass index, kg/m^2	31.83±7.01	32.87±7.02	29±6.26	0.005
Body surface area, m^2	1.98±0.26	2.02±0.25	1.9±0.25	<0.001
Female sex, %	66.90	64.20	74.30	0.279
Race or ethnicity, %				
White	34.40	33.30	37.10	0.686
Black	60.90	61.30	60	0.894
Hispanic	2.30	2.10	2.90	0.807
Hypertension, %	83.80	81.10	91.40	0.154
Hyperlipidemia, %	76.90	77.90	74.30	0.665
Diabetes, %	30.80	33.70	22.90	0.235
Heart failure, %	24.60	27.40	17.10	0.230
Tobacco use (current), %	10	10.50	8.60	0.742
Chronic kidney disease, %	11.50	12.60	8.60	0.520
Peripheral artery disease, %	4.60	5.30	2.90	0.562
Carotid artery disease, %	3.80	5.30	0	0.166
Prior PCI, %	16.90	20	8.60	0.123
Prior CABG, %	2.30	3.20	0	0.287
Prior stroke, %	16.20	15.80	17.10	0.852
Prior myocardial infarction, %	22.30	25.30	14.30	0.182
CCS Angina Score 3 or 4, %	31	30	33.30	0.782
Noninvasive ischemia evidence, %	25.40	28.40	17.10	0.190
Unstable angina, %	12.30%	10.50%	17.10%	0.308
Ejection fraction, %	56.12±9.43	56.9±7.65	54.14±12.84	0.285
Outpatient	70	71.60	65.70	0.517
Inpatient	30	28.40	34.30	0.517
Preprocedure medications, %				
Aspirin	49.20	47.40	54.30	0.484
Clopidogrel	7.70%	8.40	5.70	0.607
Ticagrelor	3.10	3.20	2.90	0.93
β blockers	45.40	49.50	34.30	0.123
Calcium channel blockers	40.80	37.90	48.60	0.272
Nitrates	20.80	24.20	11.40	0.111
Ranolazine	6.20	8.40	0	0.076
High-intensity statin	37.70	40	31.40	0.371
Moderate-intensity statin	24.60	28.40	14.30	0.097
Diuretics	32.30	35.80	22.90	0.162

CABG indicates coronary artery bypass grafting; CCS, Canadian Cardiovascular Society; CMD, coronary microvascular dysfunction; and PCI, percutaneous coronary intervention.

higher in CMD-positive patients (77.8±18.9 versus 89.4±15.7 cm^3/m^2; *P*=0.001).

Coronary and Microcirculation Hemodynamic Assessment Details

Table 2 outlines invasive hemodynamic assessment results for coronary microvascular circulation. Compared with CMD-negative patients, CMD-positive patients had a significantly higher mean index of microcirculatory resistance (37.66±20.32 versus 13.07±5.3; *P*<0.001) and a lower mean coronary flow reserve (1.94±0.8 versus 3.64±2.0; *P*<0.001). No significant differences existed between the 2 groups with respect to fractional flow reserve and resting full-cycle ratio. These hemodynamic results demonstrate a true CMD-positive cohort based on invasive testing.

Relationship Between EFV and CMD

Table 3 summarizes the logistic models of EFV and EFVi separately. The univariate regression analysis

Table 2. Hemodynamic Parameters Stratified by Coronary Microvascular Dysfunction Status

Variable	Overall (N=130)	CMD negative (N=95)	CMD positive (N=35)	*P* value
Index of microcirculatory resistance	19.69±15.78	13.07±5.3	37.66±20.32	<0.001
Coronary flow reserve	3.18±1.9	3.64±1.98	1.94±0.8	<0.001
Fractional flow reserve	0.91±0.07	0.91±0.07	0.92±0.09	0.377
Resting full-cycle ratio	0.89±0.28	0.9±0.19	0.88±0.45	0.852
Resistive reserve ratio	3.64±2.3	4.17±2.42	2.25±1.08	<0.001

CMD indicates coronary microvascular dysfunction.

demonstrated a statistically significant association between EFVi and CMD diagnosis (odds ratio, 1.037 [95% CI, 1.014–1.063]; *P*=0.003), while no significance was observed for EFV (odds ratio, 1.006 [95% CI, 0.995–1.017]; *P*=0.292). For every 10-unit increase in the EFVi, the odds of a CMD diagnosis were estimated to increase by 43.8%. Figure 2 illustrates the predicted probability of CMD diagnosis and its confidence band given EFV and EFVi on the basis of each model.

The scatter plot (Figure 3) demonstrates a positive correlation between age and the EFVi in both CMD-positive and CMD-negative patients. The regression lines for both groups are ascending, which indicates that as age increases, the EFVi also increases. The regression line of the CMD-positive group was steeper and positioned above that of the CMD-negative group, implying that on average, CMD positivity is associated with a higher EFVi at any given age.

DISCUSSION

In the present study, we investigated the association between EAT in terms of EFV and EFVi with the presence of CMD. The main findings of our study are (1) CMD-negative patients tended to have lower EFVi values than CMD-positive patients; (2) higher EFVi was associated with increased likelihood of CMD diagnosis; (3) CMD-positive patients consistently demonstrated a higher EFVi across all ages, suggesting an age-independent relationship of EFVi with CMD. These findings suggest that EAT could have a critical role in CMD development and indication for CMD assessment.

Several studies previously examined the link between EAT and CMD; our findings extend beyond previous studies demonstrating that EAT is independently directly related to CMD.[12,19–25] However, the earlier studies primarily relied on noninvasive methods to diagnose CMD (eg, echocardiography, single-photon emission CT, myocardial perfusion imaging, or positron emission tomography scans). Noninvasive techniques to assess coronary microvascular physiology are inferior to invasive techniques using pressure and Doppler/thermodilution flow wires.[26–28] In parallel, noninvasive techniques, including computational fluid dynamics and quantitative perfusion analysis, are still under development and have not reached full maturity.[29] Our study is the first of its kind, addressing this gap by using a more reliable, quantitative measure with pressure/thermodilution wire technology used during cardiac catheterization.

Table 3. Association of Epicardial Fat Volume Index with CMD

Variable	Odds ratio	95% CI	*P* value
Epicardial fat volume, cm^3	1.006	0.995–1.017	0.292
Epicardial fat volume index, cm^3/m^2	1.037	1.014–1.063	0.003

CMD indicates coronary microvascular dysfunction.

Our analysis reveals that the likelihood of CMD diagnosis increases as EFVi increases. This finding further clarifies that EFV needs to be adjusted by body surface area to be a risk factor for CMD, as previous clinical studies suggest.[12,24,30] Epicardial fat is an active tissue, secreting both proinflammatory and anti-inflammatory mediators.[10] An accumulated EAT (increased EFV) may become more inflammatory, potentially leading to local and systemic inflammation through the release of proinflammatory cytokines.[31,32] This inflammation could directly affect the coronary microcirculation and contribute to the development of CMD. Increasing evidence of the role of inflammation in the development of CMD has been introduced in the literature.[33] Chronic inflammatory diseases such as systemic lupus erythematosus, rheumatoid arthritis, and systemic sclerosis have been also linked with CMD.[34] Furthermore, increased EFV is linked to CAD, atrial fibrillation, and severe aortic valve stenosis independent of traditional risk factors.[8,9,35]

It is important to note that our study also found CMD-negative patients to be younger (on average) than the CMD-positive group, mirroring existing research that shows an association between aging and CMD.[36] As humans age, the ability of the coronary vessels to dilate decreases due to increased minimal microvascular resistance. This is perhaps partially explained by a potential age-related increase in EFV, with studies showing 22% more thickness in people aged >65 years.[37,38]

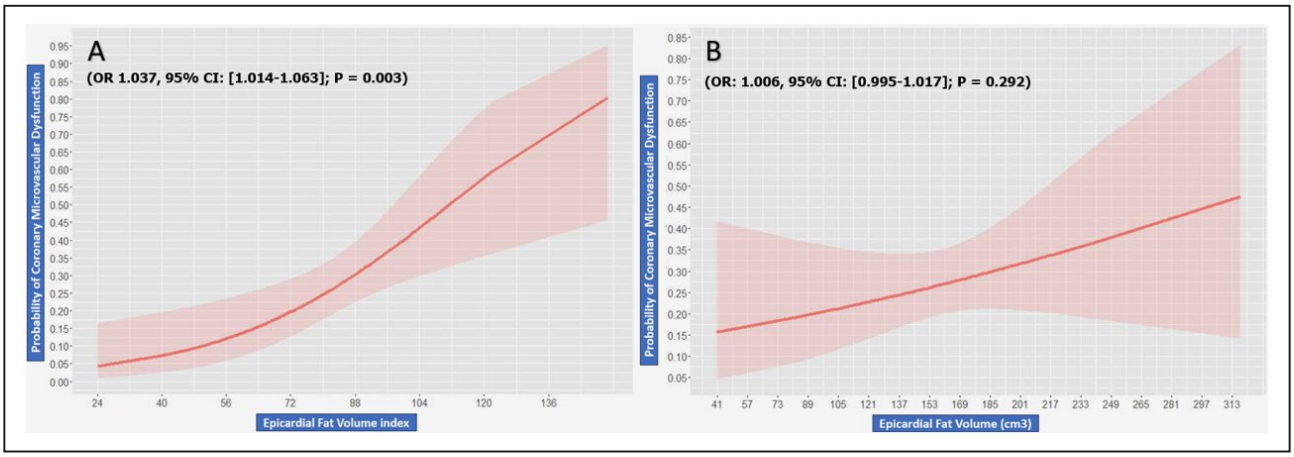

Figure 2. Relationship between epicardial fat measures [epicardial fat volume (A) epicardial fat volume index (B)] and predicted probability of coronary microvascular dysfunction.
A, This graph displays the predictive modeling results illustrating the correlation between the epicardial fat index and the probability of coronary microvascular dysfunction diagnosis. The red line represents the predicted probability curve. The shaded pink area around the line represents the 95% CI. **B**, This graph displays the predictive modeling results illustrating the correlation between the epicardial fat volume and the probability of coronary microvascular dysfunction diagnosis. The red line represents the predicted probability curve. The shaded pink area around the line represents the 95% CI. OR indicates odds ratio.

The process of aging itself can also affect the structure and function of epicardial fat.[39] Furthermore, CMD appears to manifest differently depending on the severity of obesity.[40] In general obesity, classical CMD is more common and is characterized by reduced blood flow during increased heart demand.[41] However, in advanced obesity, endogenous CMD becomes more prevalent, and elevated resting blood flow paradoxically limits the heart's ability to further increase flow when needed.[41,42] Recognizing these distinct CMD subtypes and their association with obesity severity may prove crucial in tailoring treatment strategies for this increasingly prevalent condition.

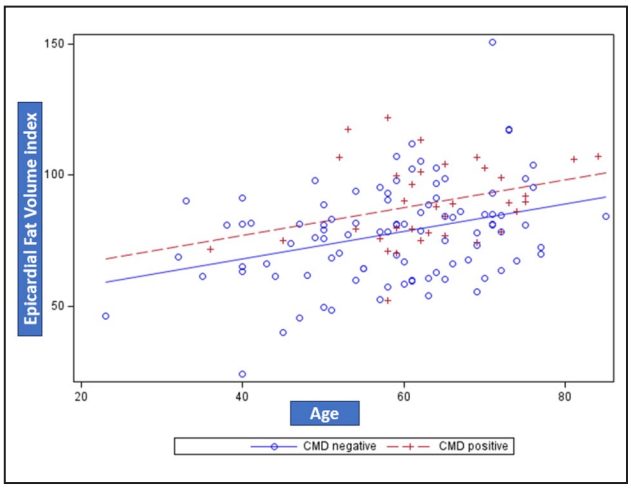

Figure 3. Correlation between age and epicardial fat volume index by CMD status.
This scatter plot illustrates the correlation between age (in years) and epicardial fat volume index for 2 groups of individuals: those with a negative coronary microvascular dysfunction (CMD) status (blue circles) and those with a positive CMD status (red pluses). The blue solid line represents the linear regression model for the CMD-negative group. The red dashed line models the trend for the CMD-positive group. CMD indicates coronary microvascular dysfunction.

Beyond just a risk factor, EAT is, in fact, a promising therapeutic target given its responsiveness to medications such as statins, glucagon-like peptide 1 receptor agonists, and sodium–glucose cotransporter 2 inhibitors. Studies have shown that these medications can reduce EAT, with glucagon-like peptide 1 receptor agonists and sodium–glucose cotransporter 2 inhibitors more effective than statins in this regard.[43–48] Interestingly, adding the antidiabetic medication pioglitazone to statin therapy further reduced EAT inflammation in metabolic syndrome patients.[47] Lifestyle modifications (eg, exercise and weight management) are also linked to reduced EAT levels,[49,50] but further research is needed to determine whether interventions specifically targeting EAT reduction are potentially effective for treating or preventing CMD.

Limitation

This study has several limitations that must be considered. First, its retrospective design introduces inherent selection bias. Second, it is based on data from only 2 medical centers and involves a relatively small cohort. Third, CT attenuation variability is influenced by equipment manufacturer, performance, and scan parameters, and guidelines for quantifying EAT currently do not exist. Fourth, acetylcholine provocation testing, the gold standard for assessing coronary spasm, was not included in the diagnostic protocol. Finally, the

absence of available follow-up data prevents the evaluation of outcomes.

CONCLUSION

Our findings suggest that elevated EFVi in patients with chest pain and normal coronary CT angiogram could serve as a valuable indicator for further investigation of the microvasculature, potentially leading to earlier diagnosis and targeted management of CMD. Further studies in larger cohorts are needed to confirm the association of EAT with CMD and investigate therapeutic targets to prevent CMD.

ARTICLE INFORMATION

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Disclosures

Dr Chitturi is a consultant for Glass Health. Dr Waksman is on the Advisory Board for Abbott Vascular, Boston Scientific, Medtronic, Philips IGT, Pi-Cardia Ltd.; consultant for Abbott Vascular, Append Medical, Biotronik, Boston Scientific, JC Medical, MedAlliance/Cordis, Medtronic, Philips IGT, Pi-Cardia Ltd., Swiss Interventional/SIS Medical AG, Transmural Systems Inc.; institutional grant support: Biotronik, Medtronic, Philips IGT; and investor: Append Medical, Pi-Cardia Ltd., Transmural Systems Inc. Dr Hashim is on the Advisory Board and speaker for Abbott Vascular, Boston Scientific, and Philips IGT. Dr Case is a speaker for Asahi Intecc USA and Zoll Medical. The remaining authors have no disclosures to report.

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