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Original article

Relation of epicardial fat thickness and brachial flow-mediated vasodilation with coronary artery disease

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ABSTRACT

Objective: The purpose of this study is to investigate the presence of a statistical association between epicardial fat thickness (EFT) and coronary artery disease (CAD) and between flow-mediated vasodilation (FMD) and CAD.
Methods: We measured the EFT and FMD in 64 subjects with suspected stable angina pectoris. The patients were separated into two groups according to their coronary angiography results: 34 patients with CAD and 30 patients with normal coronary arteries (NCA).
Results: EFT was significantly higher in the patients with CAD than the NCA group (6.43 ± 0.90 mm vs. 5.35 ± 0.75 mm, $p < 0.001$) while FMD was significantly lower in the patients with CAD than those in the NCA group ($6.41 \pm 2.51\%$ vs. $8.33 \pm 3.45\%$, $p = 0.015$). No significant correlation was found between EFT and FMD. After adjustment for EFT, FMD, age, sex, ejection fraction, glucose, and low-density lipoprotein cholesterol through multivariate logistic regression analysis, EFT (odds ratio: 6.325, 95% confidence interval 2.289–17.476, $p < 0.001$) and age (odds ratio: 1.093, 95% confidence interval 1.008–1.185, $p = 0.032$) remained significant predictors of CAD. A cut-off value of EFT $\geq$ 5.8 mm predicted the presence of CAD with 77% sensitivity and 70% specificity.
Conclusion: An echocardiographic EFT assessment is independently associated with the presence of CAD. Thus, EFT may be helpful in cardiometabolic risk stratification and therapeutic interventions.

Introduction

Epicardial adipose tissue is the source of several endocrine and inflammatory mediators [1]. Epicardial fat may play a central role in the pathogenesis of cardiovascular disease mediated by its inflammatory properties [2–5]. Therefore, visceral fat predicts an unfavorable cardiovascular and metabolic risk profile in humans, and an echocardiographic assessment of epicardial fat thickness (EFT) is a reliable marker of visceral adiposity. A possible association between epicardial adipose tissue and atherosclerosis has been shown in certain recent studies [6–10]. Flow-mediated vasodilation (FMD) evaluates endothelium-dependent vasodilation, is a reliable marker of arterial endothelial dysfunction and is related to coronary artery disease (CAD). Endothelial dysfunction results from functional changes, which are characterized by vasospasm, coagulation abnormalities, and increased vascular proliferation, and is reported to be the initial step in atherosclerosis [11–13]. Peripheral endothelial function can be non-invasively evaluated by the measurement of the FMD of the brachial artery using high-resolution ultrasound methods [14,15].

Concomitant evaluation of EFT and FMD in patients with suspected stable angina pectoris (SAP) has not previously been investigated. In this study we evaluated the EFT and FMD in subjects with and without CAD.

Methods

Study population

In this observational study, we enrolled 64 consecutive patients (40 men, mean age 56.9 ± 11.2 years) with suspected SAP, who underwent a coronary angiography. The patients' histories were recorded, and all patients underwent a complete physical examination. The patients who had a history of established heart disease, hypertension, known diabetes, overt liver disease, obesity [body mass index (BMI) $\geq$30], cancer, chronic renal disease, alcohol or drug abuse, and thyroid problems were excluded from the study. Moreover, those patients whose transthoracic echocardiographic

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imaging produced inadequate data for the measurement of their EFT were also excluded from the study. All participants underwent transthoracic echocardiography and FMD examinations. Informed consent was obtained from all participants in writing, and the study was conducted based on the approval of the institutional review board.

Coronary angiography technique and data

Coronary angiographies were performed using the Judkins technique with femoral artery access, and the angiograms were visually evaluated by two interventional cardiologists, who were blinded both to the study plan and each other. A thorough review of each index coronary angiogram established the location of the lesions and the percentage of stenosis among all of the coronary lesions. CAD was defined as >50% luminal diameter stenosis of at least one major epicardial coronary artery [16]. The patients were separated into two groups according to their coronary angiography results: 34 patients with CAD and 30 patients with normal coronary arteries (NCA).

Echocardiogram and epicardial fat measurement

All participants underwent transthoracic echocardiography imaging using an echocardiograph equipped with a broadband transducer (Vivid S6, GE Vingmed Ultrasound, Horten, Norway). Measurements were obtained from the long-axis and apical four-chamber view according to standard criteria. The echocardiographic images were entered into a computerized database (EchoPac). The offline measurements of EFT were performed by two cardiologists who were unaware of the patient's clinical data. The echocardiograms of 20 patients were randomly selected, and a second measurement of the EFT was performed two weeks later in order to assess the inter-observer and intra-observer variability. The inter-observer and intra-observer variabilities of the EFT were found to be 3.8% and 3.5%, respectively. The echocardiographic assessments of the EFT were measured according to the method previously described by Iacobellis et al. [17]. The epicardial fat was identified as an echo-free space in the pericardial layers on the two-dimensional echocardiography [18,19]. The maximum EFT was measured at the point on the free wall of the right ventricle along the midline of the ultrasound beam, perpendicular to the aortic annulus. This was determined to be the anatomic landmark at the end-diastole in three cardiac cycles.

Measurement of flow-mediated vasodilation

The ultrasonographic evaluations of the patients' endothelial function and flow-mediated endothelial-dependent vasodilation were effectuated by FMD measurement in the brachial artery of the non-dominant arm. The validity of the method has been confirmed in previous studies [20,21]. FMD test was performed before coronary angiography. An experienced vascular sonographer, who was blinded to the patients' information, performed an ultrasound examination using a Vivid S6 Ultrasound System (GE Vingmed Ultrasound) with a 12-MHz linear array transducer. Briefly, the patients were instructed to lie quietly in a supine position for 10 min before the study. All studies were performed in a temperature-controlled room (20–25 °C). Arterial flow was interrupted for 5 min by a cuff placed on the proximal forearm at whichever occlusion pressure would be higher, i.e. 200 mmHg or 50 mmHg + systolic blood pressure. The brachial artery was scanned in a longitudinal section, the focus zone was set to optimize images of the lumen–arterial wall interface, and the machine operating parameters were not changed during the rest of the study. Measurements were taken from the anterior to posterior "m" line at the end-diastole, incident with the R-wave on the electrocardiogram. Three cardiac cycles were analyzed for each scan, and the measurements were averaged. Arterial diameter was measured 60 s after cuff deflation. Endothelium-dependent, post-ischemic FMD was determined by the maximal brachial artery diameter after exactly 60 s of reactive hyperemia, compared with the baseline vessel diameter, and was expressed as a percentage of FMD. The two cardiologists who were blinded to the participants' clinical data interpreted the ultrasound results using an offline method. The intra- and inter-observer variability of the FMD were calculated in 20 patients by plotting the patients' FMD estimates from each measurement against the estimates by two independent measurements. The standard error of the estimate was calculated using this plot. The intra- and inter-observer variability were 4.6% and 5.3%, respectively.

Anthromorphometry and laboratory tests

On admission, blood samples were obtained to measure the patients' glucose, creatinine, total cholesterol, triglycerides, low-density lipoprotein-cholesterol (LDL-C), and high-density lipoprotein-cholesterol levels (HDL-C), which were assayed using routine laboratory techniques. BMI was defined as weight (kg) divided by the square of height (m), and waist circumference was recorded as the average of two measurements while the subject was standing at midpoint between the lowest rib and the iliac crest.

Statistical analysis

A statistical analysis was carried out using SPSS for Windows version 15.0 (SPSS Inc., Chicago, IL, USA). All variables were tested for the normal distribution using the Kolmogorov–Smirnov test. Continuous variables were expressed as mean ± SD, and categorical variables were expressed as numbers and percentages. Student's *t*-test or the Mann–Whitney *U*-test were used for the continuous variables, and the χ^2 test was used for the categorical changes. The relationships between the variables were examined with Pearson's correlation coefficients. The cut-off value of the EFT for predicting the presence of CAD with corresponding sensitivity and specificity was estimated by the receiver operating characteristic (ROC) curve analysis. Conventional risk factors of CAD (age, gender, glucose, and LDL-C) and all variables showing significance values $p < 0.1$ on univariate analysis (EFT, FMD, and ejection fraction) were included in the multivariate model. Statistical significance was based on a value of $p < 0.05$.

Results

The clinical and laboratory characteristics are shown in Table 1. All clinical and anthropometric parameters, except EFT and FMD, were similar between the two groups. EFT was significantly higher in the patients with CAD than the NCA group (6.43 ± 0.90 mm vs. 5.35 ± 0.75 mm, $p < 0.001$). FMD was significantly lower in the patients with CAD than those in the NCA group (6.41 ± 2.51% vs. 8.33 ± 3.45%, $p = 0.015$). Both groups were similar in terms of biochemical analysis. No significant correlation was found between EFT and FMD in the whole sample ($r = -0.232$, $p = 0.065$), in patients with CAD ($r = 0.052$, $p = 0.771$), and in patients with NCA ($r = -0.209$, $p = 0.267$).

After adjustment for EFT, FMD, age, sex, ejection fraction, glucose, and LDL-cholesterol through multivariate logistic regression analysis, EFT (odds ratio: 6.325, 95% confidence interval 2.289–17.476, $p < 0.001$) and age (odds ratio: 1.093, 95% confidence interval 1.008–1.185, $p = 0.032$) remained significant predictors of CAD whereas the adjusted association between FMD and CAD was

Table 1
Baseline characteristics of patients in the NCA and CAD groups.

	NCA ($n=30$)	CAD ($n=34$)	p-Value*
Mean age (years)	54.8 ± 10.3	58.7 ± 11.8	0.168
Male, n (%)	16 (53)	24 (70)	0.155
Waist circumference (cm)	83.4 ± 9.0	84.8 ± 8.2	0.520
BMI (g/m^2)	26.0 ± 3.3	26.1 ± 2.8	0.953
Smoking, n (%)	5 (17)	6 (18)	0.917
Systolic blood pressure (mmHg)	116.8 ± 11.9	116.8 ± 11.9	0.982
Diastolic blood pressure (mmHg)	71.3 ± 8.0	72.4 ± 7.5	0.602
Ejection fraction (%)	60.5 ± 3.3	58.5 ± 3.8	0.053
Glucose (mg/dl)	100.0 ± 13.2	101.2 ± 12.7	0.702
Creatinine (mg/dl)	0.8 ± 0.2	0.8 ± 0.2	0.242
Total cholesterol (mg/dl)	185.0 ± 39.1	185.9 ± 43.5	0.937
LDL-cholesterol (mg/dl)	106.0 ± 31.8	117.0 ± 36.3	0.205
HDL-cholesterol (mg/dl)	37.5 ± 10.0	36.3 ± 8.9	0.639
Triglycerides (mg/dl)	202.4 ± 124.9	162.5 ± 73.6	0.133
Epicardial fat thickness (mm)	5.35 ± 0.75	6.43 ± 0.90	<0.001
Flow mediated vasodilation (%)	8.33 ± 3.45	6.41 ± 2.51	0.015

Abbreviations: NCA, normal coronary artery; CAD, coronary artery disease; BMI, body mass index; LDL, low density lipoprotein; HDL, high density lipoprotein.
Values are given as mean ± SD or n (%).
* Student's t-test; Mann–Whitney U-test; Chi-square test.

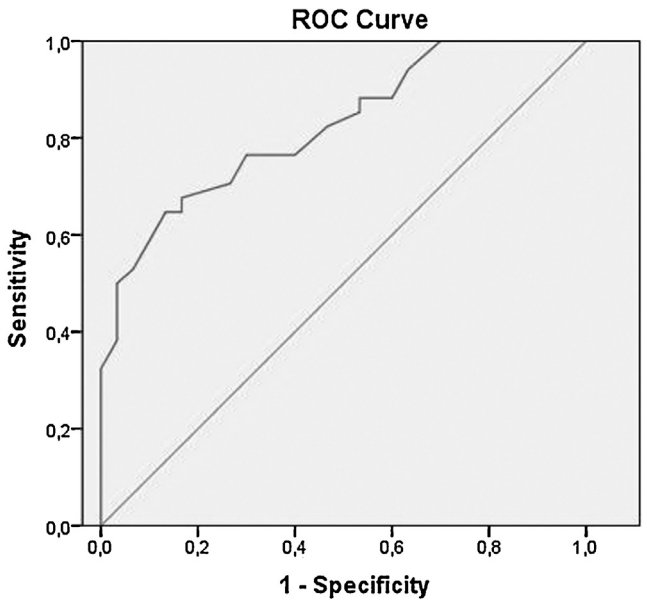

Fig. 1. Receiver operating characteristic (ROC) curve analysis of the epicardial fat thickness level predicting coronary artery disease in patients with stable angina.

not statistically significant ($p=0.057$) (Table 2). Using ROC analysis, a level of EFT ≥ 5.8 predicted the presence of CAD with 77% sensitivity and 70% specificity (ROC area under curve = 0.823, 95% confidence interval = 0.723–0.922, $p<0.001$) (Fig. 1).

Discussion

The present study demonstrated that increased levels of EFT are an independent predictor for the presence of CAD. In addition, FMD was significantly lower in the patients with CAD than those in the NCA group, whereas in the multivariate analysis, FMD was not found to be a predictor of CAD. Moreover, our study showed that a level of EFT ≥ 5.8 mm predicted the presence of CAD with 77% sensitivity and 70% specificity. To the best of our knowledge, this is the first study to report on the concomitant relationship between the EFT, FMD, and CAD.

Epicardial fat is thought to promote the development and progression of coronary atherosclerosis. Elevated inflammatory infiltrate has been described in the epicardial fat of subjects with CAD [1]. The paracrine or vasocrine secretion of epicardial inflammatory molecules contributes to the metabolic and inflammatory milieu that also promotes atherogenesis [1]. In vitro studies have shown that the paracrine dialogs between human adipocytes and the inflammatory cells present in adipose tissue promote an increased synthesis of numerous biomolecules, leading to a low-grade inflammatory microenvironment [5]. These conditions most likely promote plaque formation and coronary stenosis.

Recently, scientific and clinical interest in epicardial fat has increased [22–25]. The study by Shemirani and Khoshavi [26] highlights the correlation between echocardiographic EFT and the severity of coronary artery disease. Ahn et al. [27] showed that EFT was thicker in subjects with CAD than in those without CAD and that it might provide additional information for assessing CAD risk and predicting the extent and activity of CAD. The results of Comert et al. [28] found a significant correlation between slow coronary flow, defined as an early phase of atherosclerosis, and EFT while Iacobellis and Sharma [24] showed that an echocardiographic assessment of epicardial fat can serve as a new index of cardiac and visceral adiposity. Moreover, epicardial fat is known to be clinically correlated with abdominal visceral adiposity measured by the echocardiographic presence of atherosclerosis [29,30] and CAD [31].

Table 2
Multivariate logistic regression analysis to assess predictors of presence of coronary artery disease.

	Odds ratio	95% confidence interval	p-Value
EFT	6.325	2.289–17.476	<0.001
FMD	0.763	0.577–1.009	0.057
Age	1.093	1.008–1.185	0.032
Sex	5.030	0.949–26.666	0.058
Ejection fraction	0.895	0.710–1.128	0.346
Glucose	0.965	0.904–1.030	0.288
LDL-cholesterol	1.017	0.995–1.040	0.132

Abbreviations: EFT; epicardial fat thickness; FMD; flow mediated vasodilation; LDL; low density cholesterol.

Endothelial dysfunction promotes CAD and has been shown to precede angiographic or ultrasonic evidence of atherosclerosis [12,32,33]. In patients with endothelial dysfunction, the balance between vasoconstriction and vasodilation is disturbed, and permeability, platelet aggregation, leukocyte adhesion, and the generation of cytokines are increased [34–36]. Endothelial dysfunction is frequently present in patients presenting with stable CAD. FMD evaluates endothelium-dependent vasodilation, is a reliable marker of arterial endothelial dysfunction, and is related to CAD. It provides important prognostic data in addition to more traditional cardiovascular risk factors from which FMD has been used to evaluate endothelial function [37–39]. A decreased FMD value could be one of the predictors of CAD in patients with stable angina. This result agrees with a previous report that showed impaired FMD to be a marker of the preclinical phase of overt CAD [33].

The main difference between our study population and previous cohorts was the inclusion of patients with only SAP. Comorbidities and medication that could interfere with FMD values were excluded, and this enables a better evaluation of FMD and SAP. Furthermore, FMD and EFT have not been simultaneously evaluated in patients with CAD. A previous study, conducted by Mazzoccoli et al. [40] of patients with idiopathic deep vein thrombosis found impaired FMD and increased EFT thickness. The authors concluded that these alterations might predict an increased risk of cardiovascular events.

The epicardial adipose tissue reflects the visceral adiposity, which has been proposed as a new cardiometabolic risk factor [22]. Epicardial fat may play a central role in the pathogenesis

of cardiovascular disease mediated by its inflammatory properties [2–5]. FMD is a reliable marker of arterial endothelial dysfunction and is related to CAD. The aim of this study was to investigate whether two markers of cardiovascular risk (FMD and epicardial fat) were associated with CAD. Although, FMD and EFT were associated with CAD, we could not find any relationship between EFT and FMD.

Endothelial dysfunction and epicardial adipose tissue contribute to risk assessment possibly in different ways reflecting a cumulative risk associated with CAD. Increased pericoronary fat and local visceral adipose tissue may increase the development of atherosclerosis in the underlying coronary vasculature. Epicardial adipose tissue secretes proinflammatory mediators including interleukin-1B, interleukin-6, monocyte chemotactic protein, and tumor necrosis factor, and promotes CD45 mRNA expression with elevated macrophage and mast cell infiltration in the adventitia of coronary lesions [1,41,42]. Therefore, epicardial fat may directly promote regional atherosclerosis from the adventitial side. Endocrine effect through adventitial vasa vasorum, and direct paracrine effect that atherogenic signals diffuse in interstitial fluid across the vessel wall may be a reason for the greater predictive value of fat thickness in detecting CAD. As a result, EFT and age were better predictors of the presence of CAD than FMD or the other coronary risk factors in patients with SAP.

Study limitations

Our study has several limitations. We included subjects meeting specific criteria of inclusion. This allowed us to compare well-matched groups, but the results obtained may not be applied to the general population. Echocardiographic EFT is a linear measurement and therefore may not reflect the total epicardial fat volume that varies at different locations around the myocardium. We believe that echocardiography is accurate, easier, readily available, and less expensive than magnetic resonance imaging and computed tomography which are the gold standard diagnostic methods for assessing EFT and volumes.

Conclusion

Increased EFT and altered endothelium-dependent vasodilation are markers of increased cardiovascular risk. The data obtained in our study show that subjects with SAP have an impairment of FMD and an increase in EFT. EFT was a better predictor of the presence of CAD than FMD in patients with SAP. The evaluation of EFT might represent valuable and reliable tools to refine clinical risk stratification in patients with CAD.

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