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Epicardial fat thickness: A surrogate marker of coronary artery disease – Assessment by echocardiography

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ABSTRACT

Objective: Epicardial fat is considered as indicator of cardiovascular risk. Several studies have tested the association between epicardial fat thickness (EFT) and coronary artery disease. The aim of our study is to test the hypothesis that echocardiographic EFT is a marker of coronary artery disease.

Methods: One hundred and ten patients (70 males and 40 females with mean age of 51.5 ± 10.6 and 52.6 ± 9.6, respectively) admitted for coronary angiogram underwent assessment of epicardial fat thickness by echocardiography. Routine clinical examination, evaluation of risk factor profile, and anthropometric variables were also done. Epicardial fat thickness was measured on the free wall of right ventricle in parasternal long- and short-axis views at end-systole for 3 cardiac cycles.

Results: Mean epicardial fat thickness in angiographically normal patients and acute coronary syndromes were 4.4 ± 1.2 and 6.9 ± 1.9, respectively. Epicardial fat thickness in males and females were not statistically different. Burden of coronary arterial lesions denoted by Gensini score shows linear association with epicardial fat thickness and the severity of the coronary disease.

Conclusion: Epicardial fat is independently and linearly associated with CAD and its severity.

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1. Introduction

The heart and vessels are surrounded by layers of adipose tissue, which is a complex organ composed of adipocytes, stromal cells, macrophages, and a neuronal network, all nourished by a rich microcirculation. The layers of adipose tissue surrounding the heart can be subdivided into intra- and extrapericardial fat. Their thicknesses and volumes can

be quantified by echocardiography and computed tomography or magnetic resonance imaging, respectively.[1,2] The term extrapericardial fat defines thoracic adipose tissue external to the parietal pericardium. It originates from primitive thoracic mesenchymal cells and thus derives its blood supply from noncoronary sources.[3] Intrapericardial fat is further subdivided into epicardial and pericardial fat. Anatomically, epicardial and pericardial adipose tissues are clearly different.[3,4] Epicardial fat is located between the outer

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wall of the myocardium and the visceral layer of pericardium.

Pericardial fat is anterior to the epicardial fat and therefore located between visceral and parietal pericardium. Much of the importance within the epicardial fat is its anatomical closeness to the myocardium and the fact that the two tissues share the same microcirculation.

The epicardial fat layer originates from mesothelial cells and hence obtains its vascular supply from the coronary arteries. It has been shown that epicardial fat is metabolically active and a source of several adipokines and inflammatory cytokines, and there seems to be potential interactions through paracrine or vasocrine mechanisms between epicardial fat and myocardium.[5–8] This is clearly not true for the pericardial fat. Gensini scoring system is a good tool to quantify coronary stenosis.[9] Some studies correlated epicardial fat thickness with severity of coronary stenosis with conflicting results. Therefore, the aim of our study is to evaluate the hypothesis that there is a correlation between echocardiographic EFT thickness and severity of coronary artery disease.

2. Methods

2.1. Study design

The study was designed as an observational cross-sectional study. All the participants were informed of its objectives before the study and signed letter of consent in accordance with the Helsinki Declaration Standards was obtained. Our study cohort consisted of 110 patients, who underwent coronary angiography for suspected coronary artery disease.

2.2. Inclusion criteria

Patients who underwent coronary angiogram for suspected coronary artery disease and did not meet the exclusion criteria.

2.3. Exclusion criteria

Patients who had chest deformities, chronic lung disease, poor echo window, pericardial and/or pleural effusion on transthoracic echocardiography, previous coronary artery bypass graft surgery (CABG), percutaneous coronary intervention (PTCA), and chronic kidney disease were not included in the study. All patients underwent detailed history, clinical examination, anthropometric measurement, routine biochemistry, ECG, and transthoracic echocardiography. Some of the patients had already undergone exercise treadmill test.

2.4. Variables

Body mass index (BMI) was calculated as body weight in kilograms and divided by height squared. Obesity was defined as having a BMI $\geq 30 \, \mathrm{kg/m^2}$. Hypertension was defined as systolic blood pressure $\geq 140 \, \mathrm{mmHg}$, diastolic blood pressure $\geq 90 \, \mathrm{mmHg}$, or requirement for antihypertensive medication.[10] Diabetes mellitus was defined according to the criteria of the

American Diabetes Association or requirement for insulin or oral hypoglycemic drugs.[11] Hyperlipidemia was defined as total cholesterol higher than $220 \, \mathrm{mg/d}$ or triglycerides $\geq 150 \, \mathrm{mg/dl}$.[12]

2.5. Echocardiographic measurement

Transthoracic echocardiography provides a reliable measurement of EFT.

Transthoracic echocardiography for the purpose of measuring epicardial fat thickness was done within 3 days after coronary angiography. Echocardiograms were performed with a PHILIPS HD 7 instrument according to standard techniques, with subjects in the left lateral decubitus position. Echocardiographic images were recorded onto a computerized database and videotape. The offline measurement of epicardial fat thickness was performed by 2 cardiologists who were unaware of the clinical and angiographic data. We measured epicardial fat thickness on the free wall of right ventricle from the parasternal long- and short-axis views, since it allows accurate assessment.[13,14] We preferred to measure at end-systole since compression of epicardial fat layer occurs during diastole.[6] Epicardial fat was identified as an echo-free space between the myocardium and visceral pericardium. The epicardial fat thickness was measured perpendicularly on the free wall of the right ventricle at end-systole for 3 cardiac cycles. The measurement was performed at a point on the free wall of the right ventricle where the fat thickness was highest (Fig. 1). The average value from 3 cardiac cycles for each echocardiographic view was tabulated and used for the statistical analysis.

2.6. Coronary angiography

In a fasting state, coronary angiography was performed using the Judkins' technique, by the femoral or radial artery approach. The severity of coronary atherosclerotic lesions was evaluated from at least 3 projections in all the patients by modified Gensini scoring system. According to this scoring system, coronary arterial system was divided into 8 segments and the most severe luminal narrowing in each coronary segment was graded with 1 to 4 points (between 1% and 49% – 1 point; 50% and 74% – 2 points; 75% and 99% – 3 points; 100% – 4 points). Each patient was evaluated with a total score between 0 and 32 points. Each point was multiplied with separate coefficients based on vessel and its segments; these coefficients were 5 for left major coronary artery, 2.5 for proximal LAD, 1.5 for middle LAD, 1.5 for distal LAD, 1 for diagonal LAD, 2.5 for proximal circumflex artery, 1 for marginal obtuse and posterolateral branch, 1.5 for right proximal coronary, 1 for posterior descending artery, and 0.5 for others. The points were added and total Gensini points were calculated for each patient.[5] Patients who had normal coronary angiograms and negative treadmill test were used as controls.

2.7. Statistical analysis

Statistical analysis was done using SPSS 13.0 for windows. Continuous variables are expressed as means $\pm$ SD and categorical variables as absolute numbers and percentages. Comparisons of continuous variables were performed using
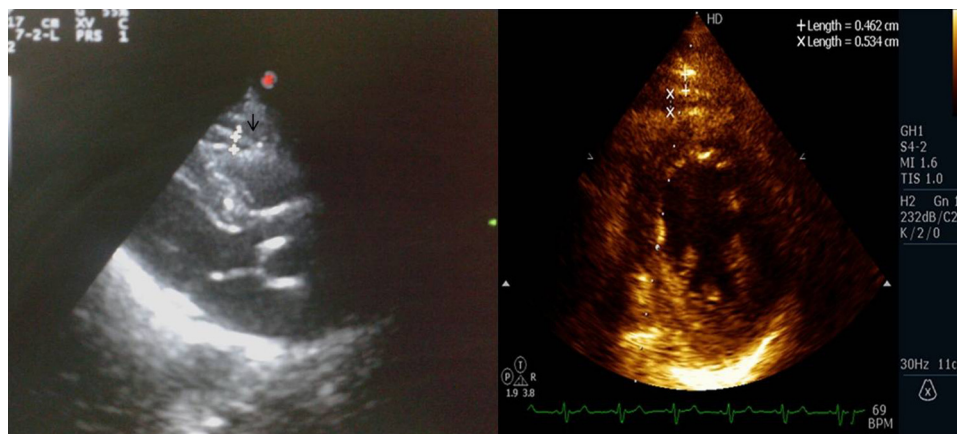
Fig. 1 – Epicardial fat thickness (EFT). Showing pericardial (thick head arrow) fat and epicardial fat (thin head arrow) in parasternal long- and short-axis views.

the unpaired Student's *t*-test and categorical variables were compared with the Chi-square test. Pearson correlation analysis was used for analysis of correlation between EFT and age, BMI, and serum lipids. The effect of EFT on the presence and severity (Gensini scoring) of CAD was assessed using analysis of covariance (ANCOVA) and Spearman's partial correlation analysis, controlling for the confounding factors including: diabetes, sex, age, smoking, dyslipidemia, and BMI. Distribution of diabetes, hypertension, and smoking in normal and CAD group was analyzed with Chi-square test. Statistical significance was set at <0.05.

3.   Results

3.1.   Demographic features

110 subjects in the range of 25–80 years were included. Mean ages of normal and CAD groups were 51.5 ± 10.6 and 52 ± 9.6 years, respectively with no statistically significant difference ($p = 0.559$). Overall, 32 (64%) and 38 (63.3%) males were in normal and CAD groups, respectively. Cardiovascular risk factors were distributed in groups. Distribution of diabetes, hypertension, smoking, dyslipidemia, and BMI in both control and CAD groups were not significantly different as per Chi-square and unpaired *t*-test. Distribution of variables like diabetes and dyslipidemia were similar in both sexes, unlike other variables (Table 1).

3.2.   EFT and clinical variables

Epicardial fat thickness varied between 0.9 and 13.5 mm. Mean of thickness in normal group was 4.4 ± 1.2 mm and in CAD group it was 6.9 ± 1.9 mm (Fig. 2) that was statistically significant ($p = 0.0001$). Additional ANCOVAs in both groups (normal and CAD), with discussion of diabetes, sex, age, smoking, dyslipidemia, and BMI, as dependent variables, showed that the differences in EFT between both groups had significantly influenced the CAD presence ($p = 0.0001$) (Table 2). Correlation between EFT and age ($p = 0.870$), and EFT and BMI ($p = 0.08$), was not statistically significant. Although Mean epicardial fat thickness was slightly higher in males, it was not statistically significant (Table 2).

3.3.   Correlation between EFT and severity of CAD

Correlation EFT with severity of CAD with Spearman's analysis (Spearman $r = 0.3$, $p = 0.0001$) is defined, but despite confounding variables again, EFT had positive correlation with the severity of coronary diseases (Gensini scoring) by controlling (partial correlation) confounding variables (Spearman $r = 0.704$, $p = 0.002$) (Table 3). Mean of Gensini scoring in CAD

Table 1 – Distribution of variables according to sex.		
Variables	Male ($n = 70$)	Female ($n = 40$)
Age	53.28 ± 10.8	51.46 ± 9.587
BMI	27.9300 (2.068)	27.4457 (1.903)
EFT	5.5575 (1.648)	5.9671 (2.304)
Hypertension	31 (44.3%)	22 (55.0%)
Dyslipidemia	21 (30.0%)	12 (30%)
Diabetus	22 (55.0%)	22 (55.0%)
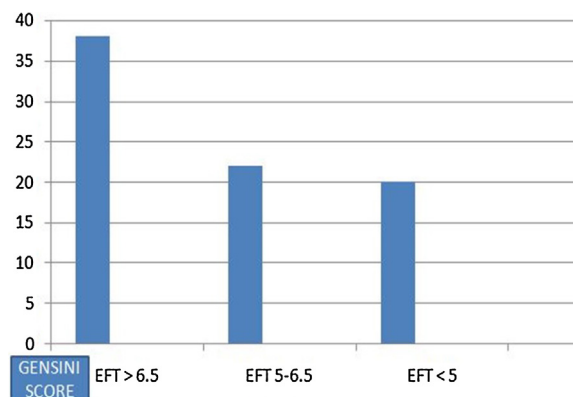
Fig. 2 – Comparison of epicardial fat thickness (EFT) with severity of coronary artery disease (Gensini score).

Table 2 – Comparison of variables in normal and coronary artery disease populations.

Variable	Normal (n = 50)	CAD (n = 50)	p value
Age in years (mean ± SD)	51.5 ± 10.6	52.6 ± 9.6	0.559
Male/female	32 (64%)/18 (36%)	38 (63%)/22 (36.6%)	0.942
Diabetes Mellitus	24 (48%)	26 (48%)	0.625
Hypertension	27 (54%)	26 (43%)	0.265
Smoking	11 (22%)	22 (36%)	0.095
Dyslipidemia	13 (26%)	20 (33%)	0.403
Eat	4.4 ± 1.2	6.9 ± 1.9	<0.0001
BMI	27.4 ± 1.7	27.7 ± 2.1	0.493

Table 3 – Spearman and Pearson correlation analysis of EFT and variables.

Variables	r	p value
Age	0.016	0.870
BMI	0.164	0.087
Gensini score	0.704	0.000

group was 30.4 ± 4.6. The correlation between EFT and severity of CAD is shown in Fig. 2.

4. Discussion

Our study reveals the association of EFT with severity of CAD. Our study also showed correlation between cardiovascular risk factors (smoking, diabetes, obesity, hyperlipidemia, age) and EFT. Even though distribution of traditional risk factors such as age, male sex, diabetes, smoking, and serum LDL had no significant difference in normal and CAD groups, the confounding effect of these risk factors was addressed by controlling these factors, in ANCOVA test and the correlation between EFT and presence of CAD was defined ($p = 0.0001$) independently. EFT thickness emerged as an independent predictor of CAD among other well-known risk factors.

Two potential mechanisms for this association have been proposed: first, EFT is a component of visceral adiposity and is related to metabolic syndrome and cardiovascular risk factors,[15–17] secondly, EFT has paracrine and endocrine functions. Iacobellis et al.[18] have pointed out that epicardial fat is clearly metabolically active and an important source of both pro- (tumor necrosis factor-α, interleukin 1, interleukin 6, nerve growth factor) and anti-(adiponectin) inflammatory cytokine production, which might significantly affect cardiac function and morphology. It can secrete numerous bioactive molecules (adipokines) such as adiponectin, resistin, and inflammatory cytokines (interleukin-1b, interleukin-6, tumor necrosis factor-α).[4,7] Interestingly, inflammatory mediators originating outside the coronary artery are also capable of including compositional changes in the inner layer of intima.[17–19]

There is a substantial amount of data demonstrating associations between increased EFT thickness and volume as assessed by echocardiography and coronary atherosclerosis. It is of note that some of the studies indicate that an increased amount of EFT is either not related to CAD or is merely a marker of visceral and overall adiposity and that adding it to the already existing cardiovascular risk assessment models does not

enhance their predictive capabilities.[20,21] More recent investigations have shown a significant association between epicardial fat and coronary artery disease by cardiac computed tomography scan.[22,23] Iacobellis et al.[8] have demonstrated an excellent correlation between epicardial adipose tissue and waist circumference, as well as the abdominal visceral adipose tissue measured by magnetic resonance imaging. These discrepancies may be to some extent the result of varying methodologies and study populations. We also showed that EFT independently was related to severity ($p = 0.042$) of CAD. The correlation between EFT thickness and the severity of CAD has been addressed previously.[24,25] However, the results of these studies are conflicting, as they did not assess patients with normal coronary arteries. Ahn et al.[26] 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.[27,28]

In this study, we defined that increased EFT correlated with severity of the coronary artery stenosis without confounding effect of dependent variables. In our study, EFT on the right ventricle varied between 0.9 and 13.5 mm. Epicardial fat thickness was almost similar in males and females (Table 4) that may be because of similar BMI in women and men.[29,30] Inflammation has been identified as a potential target for therapeutic intervention in patients with CAD.[21] Inflammatory mediators derived EFT was a favorable target for preventive intervention and novel therapeutic strategies, and these interventions (such as aspirin, angiotensin-converting enzyme inhibitor, statin, and specially exercise and weight loss) may also have anti-inflammatory effect and decreasing epicardial fat volume, but more studies are required for approving this hypothesis.[31]

Table 4 – ANCOVA result for both groups (normal and CAD) with confounding factors.

Confounding variables	[b]df	[a]F	p value
Age	1	1.197	0.278
Sex	1	10.809	0.002
Smoking	1	0.009	0.923
Hypertension	1	0.026	0.873
Dyslipidemia	1	0.001	0.971
Diabetes mellitus	1	0.005	0.946

[a] F test assumes that the errors are normally distributed and homoscedastic.
[b] df = degrees of freedom.

4.1. Study limitations

We could not confirm epicardial fat thickness using the standard MRI and CT methods. Echocardiography was a relatively simple and inexpensive method, but the accuracy and reproducibility should be further tested. In addition, as epicardial adipose tissue has a 3-dimensional distribution, 2-dimensional echocardiography may not completely assess the total amount of epicardial adiposity. Further evaluation may be necessary.

5. Conclusion

In this study, epicardial fat thickness (assessed by a simple bedside tool like transthoracic echocardiography) was higher in CAD group than in normal patients. EFT measured using this technique significantly correlated with the severity of coronary artery stenosis and can be used for risk stratification. Being a noninvasive technique, it can be repeated as many times as possible, and hence has the potential to monitor the response to life-style modification and therapy. However, a larger study involving more number of patients with longer period of follow-up is mandatory.

Conflicts of interest

The authors have none to declare.

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