Evaluation of epicardial adipose tissue by coronary multi-detector computed tomography: an independent predictor of obstructive coronary artery disease

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Abstract

Background The aim of this retrospective cross-sectional study was to investigate the relationship between epicardial adipose tissue and coronary artery disease and its severity.

Methods A total of 344 subjects with clinically suspected coronary artery disease underwent 256-slice multi-detector CT coronary angiography and were categorized as follows: no CAD, non-obstructive CAD (luminal narrowing < 50%) and obstructive CAD (luminal narrowing ≥ 50%). Calcium score was quantified using the Agatston method. Mean Epicardial adipose tissue (EAT) and mean pericoronary fat thickness (PCFT) were measured and utilized for data analysis.

Results There was a significant association between EAT thickness and PCFT with clinical risk factors of CAD including HTN, DM and obesity (*P*-value: < 0.001) and dyslipidemia (*P*-value: 0.003, *P*-value: 0.008 for EAT and PCFT, respectively). EAT thickness and PCFT were significantly higher in obstructive CAD compared to non-obstructive CAD and no CAD categories (*P*-value: < 0.001). Also, there is positive strong correlation between EAT thickness, PCFT and Calcium score (*P*-value: < 0.001). Optimal cut-off point of PCFT for estimating obstructive CAD was > 12.87 mm (sensitivity: 77.06%, specificity: 66.06% and AUC:0.76; 95%CI:0.69–0.81) via receiver operating characteristic curve. On multivariate logistic analysis which included conventional risk factors of CAD, PCFT was an independent predictor of obstructive CAD (Odds ratio:1.55; *P*-value: < 0.001).

Conclusions EAT thickness and PCFT were significantly increased in coronary artery disease. PCFT is a simple accessible marker for predicting obstructive CAD with acceptable diagnostic performance.

Keywords Coronary artery disease, CT coronary angiography, Epicardial adipose tissue, Pericoronary fat

Background

Coronary Artery Disease (CAD) is a frequent health problem and the leading cause of death worldwide [1]. Given CAD's high impact on mortality and morbidity in populations, early diagnosis and better stratification of patients are completely relevant. There is compelling evidence elucidating visceral fat as an important risk factor for CAD [2]. Epicardial adipose tissue (EAT) which is a type of visceral fat has been demonstrated to be imperatively associated with CAD [3]. Previous studies have reported that EAT is a main source of inflammatory cytokines and bioactive molecules with ultimate direct vasocrine and paracrine effect on coronary arteries with ensuing atherosclerotic disease [4]. Some researchers

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demonstrated that pericoronary adipose tissue, i.e., a subtype of EAT which is directly surrounding coronary arteries, has a pivotal role in atherogenesis via producing deleterious inflammatory adiopokines [5]. Therefore, the local fat surrounding the coronary artery (as pericoronary fat) might be influencing coronary atherosclerosis more directly and predicted significant CAD more robustly. Notably, correlation of EAT and CAD has been well documented; however, it remains debatable whether EAT can be introduced as an independent marker to predict CAD development and its severity. In recent years, temporal and spatial resolution of Multi-detector CT scan (MDCT) has been markedly improved so that MDCT is widely used as an accurate and reproducible method for measurement of EAT [6].

In this study, we investigated the correlation between EAT thickness and pericoronary fat thickness (PCFT) with the presence and severity of CAD assessed by cardiac MDCT.

Methods

Patients

A total of 344 patients with suspected CAD were enrolled in this retrospective cross-sectional study. All subjects included in our study underwent MDCT between April 2019 and February 2022 at Chamran Hospital, Isfahan, Iran. This cross-sectional study was approved by the ethics committee of Isfahan University of Medical Sciences (IR.MUI.MED.REC.1399.625). Exclusion criteria were as follows: those who had history of percutaneous coronary intervention, patients with history of coronary artery bypass graft, renal insufficiency and known history of allergic reaction to iodine-based contrast agents. Information about CAD risk factors was gathered from patient's medical records including: age, gender, body mass index (BMI) and smoking history and family history of CAD. Hypertension (HTN) was defined as systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg, or current use of medication for HTN. Diabetes was defined as Hb1Ac $\geq 6.5\%$, fasting blood glucose ≥ 126 mg/dl or patients who received glucose-lowering medications. Dyslipidemia was defined according to a widely used guideline [7].

Scanning method

All patients were imaged with a 256-slice MDCT scanner (Brilliance iCT, Philips Healthcare, Cleveland, OH, USA). For CTA, imaging parameters were set as follows: slice collimation 256×0.625 mm, tube voltage 120 kV and 200 mA tube current. At first, non-contrast enhanced scan was taken to measure calcium score according to the standard Agatston method. For coronary CT angiography, ECG-gated acquisition was done after administration of 60–80 ml Iodixanol (Visipaque 320 mg I/ml; GE healthcare, Stockholm, Sweden) directly into antecubital vein with flow rate of 5–6 cc/sec followed by 30–40 ml saline infusion. Imaging data set was transferred to an offline workstation (Philips Medical Systems) for imaging analysis.

Assessment of CAD and epicardial adipose tissue

Presence and severity of CAD were evaluated by an expert radiologist with 12 years' experience in cardiac imaging using CADRADS guideline [8]. Patients were divided into three categories: no CAD (CADRDADS:0), non-obstructive CAD (CADRADS 1 and 2; luminal narrowing less than 50%) and Obstructive CAD (CADRADS 3,4 and 5; $\geq 50\%$ luminal narrowing).

EAT thickness was measured at the basal level of the ventricles on short axis view in the most motionless phase of the cardiac cycle. At the 25%, 50–75% level of the RV and superior LV wall, measurements were made vertically to surface of the heart from visceral pericardium to outer margin of myocardium. Then, mean of these three measurements, namely 'EAT thickness' was utilized for analysis. For Pericoronary fat, as previously described [9] assessment was performed on axial view where the maximum fat thickness around LAD, LCX and RCA was measured in perpendicular fashion (in order not to overestimate thickness due to obliquity) from the outer margin of the myocardium to the visceral pericardium as well. Similarly, the mean of the three measurements was applied for data analysis as PCFT (Fig. 1).

Statistical analysis

All data were analyzed using SPSS 26.0 for windows. Relation between EAT thickness and PCFT with continuous variables and categorical variables was determined by the independent *t*-test and chi-squared test, respectively. One-way analysis of variance (ANOVA) was used in order to compare between three categories based on CAD. Spearman's correlation coefficient (*r*) was used for assessment of correlation between EAT thickness, PCFT and Calcium Score.

For determining optimal cut-off value, Receiver Operating Characteristic (ROC) curve analysis was performed. The logistic regression model via multivariate analysis was utilized to determine predictors of CAD presence and its severity considering EAT thickness and PCFT, adjusting for conventional risk factors and Calcium Score.

Results

General features

A total of 344 patients (171 males, 173 female) with a mean age of 57.54 ± 12.32 years were enrolled in this
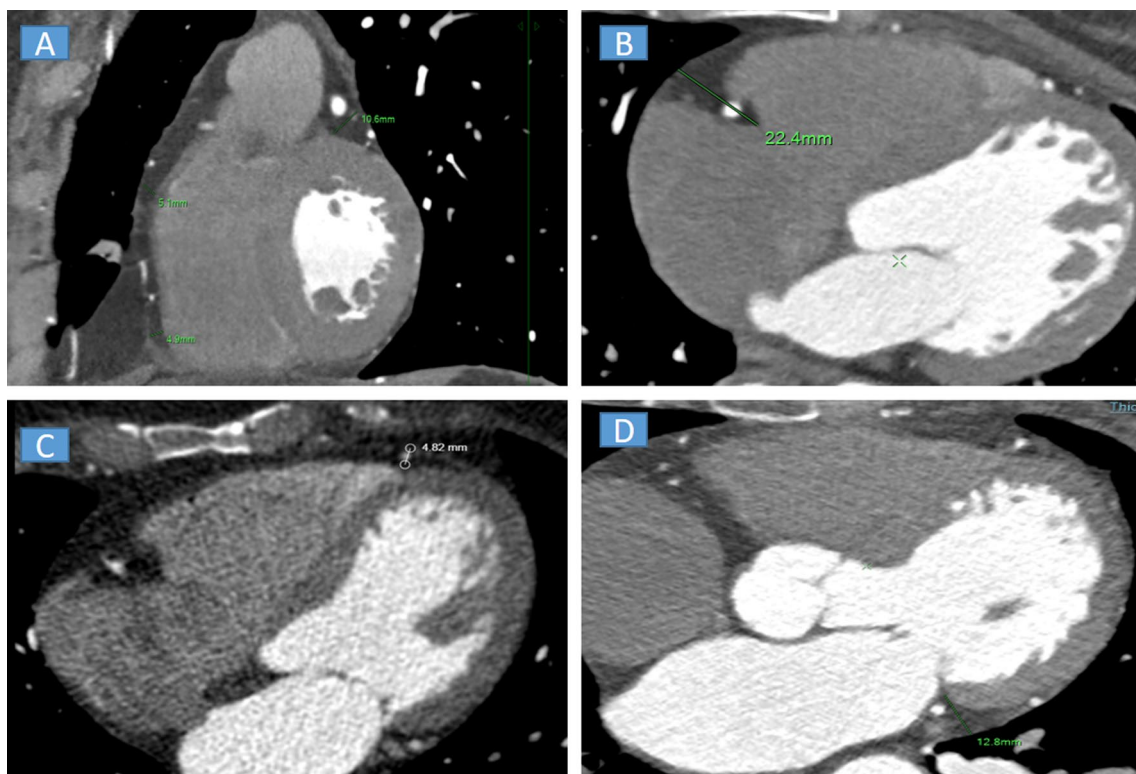
Fig. 1 Representative measurement of epicardial adipose tissue (EAT) thickness and pericoronary fat thickness (PCFT). **A** EAT thickness. **B** PCFT surrounding RCA. **C** PCFT surrounding LAD. **D** PCFT surrounding LCX. RCA, right coronary artery; LAD, left anterior descending artery; LCX, left circumflex artery

study. Among them, 133 (38.7%) subjects had obesity (BMI ≥ 30). The number of patients suffering from HTN was 178 (51.7%). With respect to DM and dyslipidemia, 87 (25.3) cases had DM and 143 (41.6%) suffered from dyslipidemia. Among the subjects, 75 (21.8%) cases were current or previous smoker and 140 (40.7%) cases had positive family history regarding CAD.

The mean Calcium Score was 153.36 ± 64.52 (ranging from 0 to 736.8). From the total, 132 (38.4%) had no CAD, 103 (29.9%) had non-obstructive CAD and 109 (31.7%) had obstructive CAD. The mean value of EAT thickness was 7.04 ± 1.94 mm while PCFT had a mean value of 12.53 ± 2.17 mm.

EAT thickness, PCFT and clinical CAD risk factors
We found EAT thickness and PCFT were significantly increased in patients with HTN, DM and obesity. There is also a significant association between EAT thickness and PCFT with dyslipidemia. We did not show any significant increase in EAT thickness and PCFT with respect to gender, smoking and family history of CAD (Table 1).

EAT thickness, PCFT and CAD
As shown in Table 2, the mean EAT thickness was significantly increased in obstructive CAD (8.17 ± 1.69 mm) compared to non-obstructive CAD (7.19 ± 1.64 mm) and no CAD (5.98 ± 1.80 mm). Considering PCFT, there was significant difference in obstructive CAD (14.14 ± 1.64 mm) compared to non-obstructive (12.45 ± 1.80 mm) and no CAD (11.25 ± 1.94 mm).

EAT thickness, PCFT and calcium score
We investigated correlation of these three biomarkers obtained from Cardiac MDCT. Calcium Score was found to be significantly correlated with EAT thickness and PCFT. EAT thickness and PCFT showed significant correlation as well (Table 3).

Diagnostic performance of EAT thickness and PCFT
We used ROC curve in order to determine best cut-off points of EAT thickness and PCFT for predicting obstructive CAD. EAT thickness and PCFT cut-off points for predicting obstructive CAD were > 8.03 mm (sensitivity, 55.05%; specificity, 71.84%) and > 12.87 mm (sensitivity,77.06%; spceficity,66.02%), respectively. Area

Table 1 The relationship between clinical characteristics and EAT thickness and PCFT

Parameters	Numbers (%)	EAT thickness		PCFT	
		Mean ± SD	*P*-value	Mean ± SD	*P*-value
Gender					
Female	173 (50.3)	7.13 ± 1.96	0.3	12.50 ± 2.06	0.8
Male	171 (49.7)	6.94 ± 1.93		12.55 ± 2.27	
HTN					
Yes	166 (48.3)	7.55 ± 1.74	< 0.001	13.09 ± 1.99	< 0.001
No	178 (51.7)	6.48 ± 2.00		11.92 ± 2.19	
DM					
Yes	87 (25.3)	7.77 ± 1.69	< 0.001	13.23 ± 1.91	< 0.001
No	257 (74.7)	6.79 ± 1.96		12.29 ± 2.21	
BMI					
< 25	211 (61.3)	6.66 ± 1.89	< 0.001	12.04 ± 2.09	< 0.001
≥ 25	133 (38.7)	7.64 ± 1.88		13.3 ± 2.07	
Dyslipidemia					
Yes	143 (41.6)	7.141 ± 1.75	0.003	12.89 ± 1.92	0.008
No	201 (58.4)	6.77 ± 2.03		12.27 ± 2.3	
Smoking					
Yes	75 (21.8)	6.94 ± 1.83	0.6	12.65 ± 2.33	0.5
No	269 (78.2)	7.07 ± 1.98		12.49 ± 2.12	
Family history					
Yes	140 (40.7)	6.90 ± 1.88	0.2	12.45 ± 2.20	0.5
No	204 (59.3)	7.13 ± 1.98		12.58 ± 2.15	

EAT, epicardial adipose tissue; *PCFT*, Pericoronary fat thickness; *HTN*, hypertension; *DM*, diabetes mellitus; *BMI*, body mass index

Table 3 Correlation Between EAT thickness, PCFT and calcium score

	Calcium score	EAT thickness	PCFT
Calcium score			
Correlation coefficient		0.438**	0.521**
Sig (2-Tailed)		< 0.001	< 0.001
Number		344	344
EAT thickness			
Correlation coefficient	0.438**		0.660**
Sig (2-tailed)	< 0.001		< 0.001
Number	344		344
PCFT			
Correlation coefficient	0.521**	0.660**	
Sig(2-tailed)	< 0.001	< 0.001	
Number	344	344	

EAT, epicardial adipose tissue; *PCFT*, pericoronary fat thickness

**Correlation is significant at the 0.01 level (2-tailed)

under the ROC curve (AUC) was 0.66(95%CI:0.59–0.73) for EAT thickness and 0.76 (95%CI:0.69–0.81) for PCFT (Fig. 2), indicating acceptable discriminatory power for PCFT.

Independent predictors of CAD

We evaluated two states by the multivariate logistic regression model: 1. Presence of CAD (no CAD vs all CAD patients) and 2. Obstructive CAD (non-obstructive CAD vs obstructive CAD). Multivariate analysis was performed by including all conventional risk factors and Calcium Score in addition to EAT thickness and PCFT. As shown in Table 4, EAT thickness and PCFT depicted an inconsistent value regarding CAD presence. For second assumption, PCFT was an independent predictor
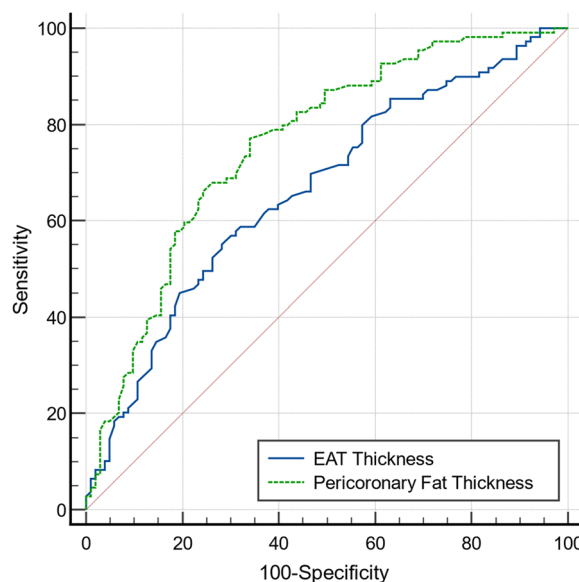

Fig. 2 ROC Curve for development of obstructive coronary artery disease by EAT thickness and pericoronary fat thickness (PCFT). The AUC for EAT thickness was 0.66 (95%CI, 0.59–0.73), and the AUC for PCFT was 0.76 (95%CI, 0.69–0.81)

Table 2 Correlation between epicardial fat and severity of CAD

Epicardial fat on CT angio	No CAD	Non-obstructive CAD	Obstructive CAD	*P*-value
Mean EAT thickness(mm)	5.98 ± 1.80	7.19 ± 1.64	8.17 ± 1.69	< 0.001
Mean PCFT(mm)	11.25 ± 1.94	12.45 ± 1.80	14.14 ± 1.64	< 0.001

CAD, coronary artery disease; *EAT*, epicardial adipose tissue; *PCFT*, pericoronary fat thickness

Table 4 Multivariate logistic regression- indicators of CAD and its severity

Parameters	Presence of CAD			Obstructive CAD		
	Odds ratio	95%CI	*P*-value	Odds Ratio	95%CI	*P*-value
Age > 55 years	1.10	1.02–1.18	0.006	1.14	0.65–2.07	0.38
Male gender	1	0.72–1.280	0.68	0.95	0.83–1.44	0.65
Diabetes	0.94	0.15–1.03	0.95	0.68	0.14–2.18	0.29
HTN	1.58	0.38–3.68	0.53	0.95	0.92–1.32	0.37
Dyslipidemia	0.68	0.36–0.93	0.04	1.17	0.88–1.96	0.49
Obesity	0.89	0.22–1.23	0.88	1.04	0.44–2.12	0.56
Calcium score	11.88	10.21–12.45	< 0.001	1.10	1.01–1.27	< 0.001
Smoking	1.29	0.4–1.32	0.25	0.41	0.17–0.98	0.04
EAT thickness	0.94	0.59–1.50	0.81	1.19	0.92–1.54	0.17
PCFT	1.28	0.82–1.99	0.28	1.55	1.22–1.98	< 0.001

CAD, coronary artery disease; *EAT*, epicardial adipose tissue; *PCFT*, Pericoronary fat thickness; *HTN*, hypertension

between non-obstructive CAD and obstructive CAD (Odds ratio:1.55; *P*-value: < 0.001).

Discussion

The current study investigated the possible relation of epicardial adipose tissue thickness, especially in the pericoronary location and its potential diagnostic performance for CAD assessed by cardiac MDCT. The main findings were as follows; (1) EAT thickness and PCFT were significantly higher in obstructive CAD compared to non-obstructive CAD and no CAD groups; (2) HTN, DM, obesity and dyslipidemia were significantly associated with higher EAT thickness and PCFT; (3) PCFT with cut-off value of > 12.87 had acceptable diagnostic performance for obstructive CAD(AUC:0.76); (4) PCFT was an independent predictor of obstructive CAD, hence, the simple quantification of PCFT can be introduced as a surrogate marker of obstructive CAD.

There is growing evidence that epicardial adipose tissue including pericoronary adipose tissue, is related to coronary artery atherosclerosis [10], however, the exact mechanisms are not fully understood. It has been proposed that epicardial adipose tissue can possibly affect CAD via producing cytokines and bioactive molecules with ensuing local inflammation and eventually atherogenesis [11]. In the current study, we found that EAT thickness and PCFT were significantly higher in the obstructive CAD group in comparison with non-obstructive CAD and no CAD groups. Some reports are in line with our results, Xie et al. [12] described that EAT thickness was higher in CAD and significantly increased during progression of CAD severity. In a study conducted by Gać et al. [13], it was indicated that positive correlation was noted between significant CAD, EAT thickness and PCFT in 80 suspected patients by coronary CT angiography. Other

studies had similar results as our data regarding correlation of EAT thickness and PCFT and obstructive CAD [14, 15]. However, You et al. [16] reported that there was no correlation between PCFT and CAD severity. A possible explanation for this inconsistency might be a different study design and measurement methods. We found a significant association between EAT thickness and PCFT with HTN, obesity, DM and dyslipidemia but not with gender, smoking and family history. Previous studies evaluating this relationship have yielded conflicting results possibly due to the target study populations [17, 18]. Mohammadzadeh et al. [17] did not show meaningful correlation between DM and dyslipidemia with EAT thickness. Furthermore, they reported that age, male gender, HTN and obesity was correlated with higher rate of EAT thickness in the Iranian population. Any relation of EAT thickness and clinical risk factors of CAD was investigated by Oka et al. [18] who did not show higher values of EAT thickness in male gender consistent with our results. Another prior study showed that PCFT was positively correlated with HTN, high BMI and age [19].

Our analysis shows strong positive correlation between EAT thickness, PCFT and Calcium score. In the study designed by Aydin et al. [20], a total of 150 subjects who underwent cardiac MDCT, larger mean PCFT was significantly associated with Calcium score. Iwasaki et al. [21] tested relation of EAT and calcium score in 651 cases by coronary CTA, and demonstrated a meaningful relationship between them. Contrary to our results, some studies didn't show any correlation between EAT and calcium score [12, 17].

We determined the best cut-off points of EAT thickness and PCFT for predicting obstructive CAD and their diagnostic performance. On AUC for estimating obstructive CAD, PCFT (AUC: 0.76) had larger area under the

curve compared with EAT thickness (AUC:0.66). This finding showed PCFT has acceptable diagnostic value for predicting obstructive CAD. Further studies with larger sample sizes can improve the discriminatory power and better clarify optimal cut-off points of PCFT. In a multivariate regression model, when conventional risk factors of CAD and Calcium Score added to EAT thickness and PCFT in order to evaluate independent predictors of CAD, results showed PCFT as an independent predictor of obstructive CAD (Odds ratio:1.55; P-value: < 0.001). This finding provides additional support to the notion that local epicardial adipose tissue surrounding coronary arteries possibly has more potent impact on atherosclerosis than global cardiac adiposity. Maimaituxun et al. [22] evaluated PCFT in 197 subjects with obstructive CAD versust non-CAD groups, and demonstrated higher value of PCFT around the left anterior descending artery (LAD) in obstructive CAD. Furthermore, this report introduced LAD-PCFT as a strong independent predictor of obstructive CAD. In the EVASCAN study which enrolled 970 patients, EAT was introduced as low power predictor of CAD with unacceptable diagnostic performance which is consistent with our results [23]. Another investigation showed that EAT volume had inconsistent predictive value for obstructive CAD [24]. On the other hand, Wu et al. [25] depicted excessive left AV groove EAT as an independent important risk factor of obstructive CAD. According to our results, PCFT can be a reliable predictor of obstructive CAD with acceptable diagnostic performance, hence, further studies with larger sample sizes with multi-center and improved methodology could help radiologists and clinicians to better stratify CAD subjects.

It is important to note that there are several limitations in our study. First, this study was performed in a single center thereby selection bias was inevitable and the sample size was relatively small. Second, it was not possible to include medications and life style interventional details of patients in our analysis. Third, our study was a retrospective cohort, so prognostic value of EAT thickness and PCFT needs to be investigated in future studies with a prospective design.

Conclusions

This study demonstrated that EAT thickness and PCFT significantly increased in obstructive CAD compared with non-obstructive CAD and no CAD subjects. Positive strong correlation was shown between EAT thickness and PCFT and Calcium score. Importantly, PCFT had acceptable diagnostic performance in order to estimate obstructive CAD and our results indicated that PCFT was an independent predictor of obstructive CAD.

Therefore, measurement of PCFT may be viewed as an indicator of obstructive CAD in patients undergoing calcium scoring and consequently could add diagnostic value of calcium score.

Declarations

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