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Assessing the Relation of Epicardial Fat Thickness and Volume, Quantified by 256-Slice Computed Tomography Scan, With Coronary Artery Disease and Cardiovascular Risk Factors

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Abstract

Background: This study aimed to investigate the association between epicardial adipose tissue (EAT) and coronary artery disease (CAD) as well as cardiovascular risk factors.

Methods: Complete medical records of subjects were reviewed and cardiovascular risk factors were recorded. Epicardial fat volume (EFV) and epicardial fat thickness (EFT) were measured using digital volumetry of acquired images using a 256-slice CT-scanner. Calcium score was measured using Agatston method in non-contrast images. After contrast administration, bolus-tract images were obtained. Coronary arteries were assessed using reconstructed images in arterial phase of contrast-enhanced images. EFV and EFT measurements were compared to computed tomography angiography (CTA) findings of coronary arteries.

Results: A total of 269 patients (Mean age: 55.5 ± 12.1, 44% female) were included. Higher means of EFT and EFV were associated with coronary artery stenosis. However, the correlation coefficients of the arterial stenosis with EFT and EFV were weak. EFV and EFT had a significant association with age ($P<0.001$, $P<0.001$ respectively), body mass index (BMI) ($P<0.001$, $P<0.001$ respectively) and hypertension ($P<0.016$, $P<0.003$ respectively). Diabetes mellitus (DM) and hyperlipidemia were not significantly associated with EFV ($P=0.069$ and 0.639 respectively) and EFT ($P=0.103$ and 0.366 respectively). EFV and EFT showed a weak correlation coefficient with calcium scoring (Spearman correlation coefficients: 0.26 and 0.22 respectively, both $P<0.001$). In multivariate logistic regression models considering coronary stenosis as dependent variable and EFV, EFT and other CAD risk factors as independent variables, EFV and EFT did not show significant *P* values and were omitted from the model by other CAD risk factors.

Conclusion: Increased EFV and EFT are associated with CAD, age, BMI and hypertension. However, no remarkable association was found between them and calcium score, hyperlipidemia or DM. These variables could weakly predict CAD in univariate models but they are not independent predictive factors for CAD in multivariate models consisting of other CAD risk factors. Hence, EFT and EFV are not independent predictors for CADs when they are considered simultaneously with other CAD risk factors.

Keywords: 256-slice CT-scan, Coronary artery disease, Epicardial fat volume, Epicardial fat thickness

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Introduction

Coronary artery disease (CAD) is the leading cause of death and a major cause of morbidity worldwide.[1] Several risk factors have been found to be associated with CAD.[1] Substantial evidence has demonstrated that visceral obesity is an independent well-established risk factor for CAD.[2,3] Epicardial adipose tissue (EAT) is a type of visceral fat that has been shown to be associated with coronary artery plaques and calcification.[4] Studies suggest that higher amounts of epicardial fat lead to coronary artery atherosclerosis by altering the expression of pro-inflammatory cytokines such as adipokine and subsequently up-regulating the inflammatory cascades.[5–7] Conventionally, transthoracic echocardiography (TTE) has been used to evaluate EAT by measuring fat thickness at the right ventricular free wall.[8] Multidetector computed tomography (MDCT) has also been used as an alternative method for measuring the amount of EAT. In contrast to TTE, MDCT is capable of digital volumetry, thus enabling more accurate quantification of EAT.[9]

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Traditionally, invasive coronary angiography (ICA) has been the standard diagnostic method for evaluation of CAD in high risk patients. However, the high accuracy of state of the art multi-slice CT scanners (64 slices and higher) in CAD detection has made coronary CT-angiography (CTA) a promising alternative for ICA.[10]

In this paper, we intended to evaluate the association of EFV and EFT (measured by a 256-slice CT-scanner) with coronary artery stenosis assessed by CTA. In addition, we have evaluated the association of these measurements with other risk factors of CAD.

Materials and Methods

This study was conducted from April 2014 to September 2015 in Rajaie hospital, Tehran, Iran. We included patients suspected of CAD who were referred for non-emergent coronary CT-angiography. Those who had a history of cardiac surgery or percutaneous coronary intervention, incomplete data regarding risk factors (age, hypertension, diabetes, hyperlipidemia etc.), renal insufficiency, anemia, and known history of allergic reactions to intravenous contrast agent were excluded. Subjects who did not consent were excluded from the study, as well. All excluded participants received the standard care. A complete record of medical conditions was gathered from enrolled patients including presence of diabetes mellitus (DM), hypertension (defined as systolic blood pressure >140 mm Hg or diastolic blood pressure > 90 mm Hg), hyperlipidemia and body mass index (BMI).

We employed a 256 Slice CT Scan facility (Somaton Definition Flash, Siemens Medical Solutions, Forchheim, Germany). Images were acquired with and without contrast administration using ECG-Gatingand standard protocol for each individual (128 × 0.6 mm section collimation, 0.27 ms rotation time, 120 kV tube voltage and 800 mAs tube current). Initially, non-contrast enhanced images were used to calculate calcium score using Agatston method. Afterwards, bolus–tract images were taken following administration of 1 to 1.5 mL/kg Iohexol (Omnipaque 300 mg/mL, Little Chalfont, United Kingdom). Reconstructed arterial phase images were processed on dedicated workstation software (Leonardo, Siemens Medical Solutions). An expert radiologist blinded to the clinical status, assessed the obtained images regarding coronary artery stenosis. Coronary stenosis was graded on the following basis: 25%–49% vessel stenosis was graded as "mild", 50%–69% stenosis was graded as "moderate" and 70%–90% stenosis was classified as "significant" stenosis. Stenosis of greater than 90% of artery diameter was classified as subtotal stenosis.

Following CTA, epicardial fat thickness (EFT) was measured in the right ventricular free wall and around the main coronary arteries (Figure 1). Epicardial fat volume (EFV) was assessed by a workstation volumetric software tool (Leonardo, Siemens Medical Solutions) that recognizes fat tissue (content with density between -30 and -200 Hounsfield unit) in the defined area between chest wall as the anterior limit and the aorta and bronchi as the posterior limit. The sum of the fat volume in all thoracic sections, excluding mediastinal and pericardial fat tissues, provided the total EF volume. EAT volume was determined by the same radiologist, blinded to the clinical condition of patients and the results of CTA.

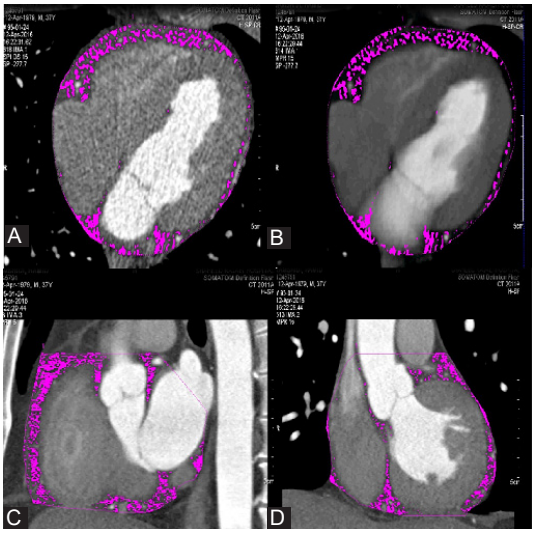

Figure 1. CT Volumetric Measurement of EFT in Transaxial View (A,B), Sagittal View (C) Coronal View(D) With Contrast Enhancement.

EFT and EFV measurements were found to be highly reproducible. The intraclass correlation coefficients (ICC) for assessing EFV and EFT by the same radiologist were 0.842 and 0.881, respectively.

Results were analyzed using STATA (version 11, Stata Corp, College Station, TX, USA). The data was presented as mean and standard deviation or numbers (%), when appropriate. Independent sample *t* test was used to evaluate the relation between EAT thickness and volume outcomes with different personal variables. One-way analysis of variance (ANOVA) was used to compare mean of EFT and EFV between patients with different severities of coronary stenosis. In order to assess the relation between EFV and EFT with numerical variables such as age, BMI, number of involved coronary arteries and calcium score, Pearson and Spearman correlation coefficients were used. The logistic regression models (univariate and multivariate) were used for predicting stenosis and significant stenosis in each coronary artery and whole-heart basis considering EFT, EFV and other associated factors [or proven risk factors] as independent variables. P value < 0.05 was considered as significant.

Results

Totally, 269 patients (150 males, 119 females) with a mean age of 55.5 ± 12.1 years (ranging from 25 to 89) were investigated during the study. The mean BMI of subjects was 27.09 ± 3.7 (ranging from 17 to 37). Among them, 132 (49.1%) cases suffered from hypertension, 106 (39.4%) suffered from hyperlipidemia and 52 (19.3%) patients had DM. The mean value for Calcium Score was 237.07 ± 8.45 (ranging from 0 to 299.7). The severity of stenosis for each coronary vessel imaged by CTA is outlined in Table 1.

EFT had a mean value of 9.03 ± 2.44 mm (ranging from 2.67 mm to 15.66 mm). The mean value for EFV was 108.8 ± 45.4 mL (ranging from 14 mL to 276 mL). Thirty-five patients had stenosis in only one artery. Twenty individuals had two-vessel stenosis and 40 individuals had three-vessel stenosis. Male participants had a significantly higher amount of EFV (119.5 ± 47.4 mL vs. 95.08 ± 38.8 mL, $P<0.001$) and EFT (8.59 ± 2.30 mm vs. 9.38 ± 2.50 mm, $P<0.001$) in comparison to female patients.

A significant association was found between EFT and CAD in left main artery (LM), left anterior descending artery (LAD), left circumflex artery (LCX) and right main coronary artery (RCA). Moreover, a significant association was revealed between EFV and CAD in LAD and LCX. The relationship between EFT and volume with coronary artery stenosis severity is outlined in Table 2.

EFT and EFV were significantly correlated with age (Pearson's correlation coefficients: 0.658, 0.598 respectively, both $P<0.001$) and BMI (Pearson's correlation coefficients: 0.758, 0.798 respectively, both $P<0.001$). Ca-score was found to be weakly correlated to EFV and EFT (Pearson's correlation coefficients: 0.273, 0.227 respectively, both $P<0.001$). Table 3 outlines the Spearman correlation coefficients between EFV and EFT with individual coronary stenosis severity, number of involved coronary arteries and number of coronary arteries with significant stenosis.

Mean EFT of hypertensive and non-hypertensive patients were 9.49 ± 2.31 mm and 8.59 ± 2.49 mm respectively. ($P<0.003$) Mean EFV of hypertensive and non-hypertensive patients were 115.6 ± 45.3 mL and 102.2 ± 44.7 mL respectively ($P=0.016$). Mean EFV of diabetic and non-diabetic participants were 111.91 ± 49.1 mL versus 106.3 ± 44.3 mL ($P=0.069$). Mean EFT of diabetic and non-diabetics were 9.53 ± 2.46 mm and 8.91 ± 2.43 mm respectively ($P=0.103$). Patients with hyperlipidemia had a mean EFV of 110.4 ± 42.1 mL while non-hyperlipidemic participants had a mean value of 107.7 ± 47.6 mL ($P=0.639$). Mean values of EFT in these groups were 9.20 ± 2.20 mm and 8.92 ± 2.59 mm, respectively ($P=0.366$).

The univariate and multivariate logistic regression models were performed on per-vessel and per-heart basis.

Table 1. Frequency of Coronary Artery Stenosis in Enrolled Patients

Artery	Stenosis Severity	Frequency	Percentage
LM	Normal	223	82.9
	Mild	30	11.2
	Moderate	8	3
	Severe	8	3
LAD	Normal	103	38.3
	Mild	57	21.2
	Moderate	27	10
	Severe	82	30.5
RCA	Normal	147	54.6
	Mild	54	20.1
	Moderate	13	4.8
	Severe	55	20.4
LCX	Normal	152	56.5
	Mild	51	19
	Moderate	10	3.7
	Severe	56	20.8

Abbreviations: LM, left main artery; LAD, left anterior descending artery; RCA, right coronary artery; LCX, left circumflex artery.

Table 2. Mean Values of EFV and EFT in Different Severities of Main Coronary Arteries and Spearman Correlation Coefficient of These Variables With Stenosis Severity in These Vessels

Artery	Stenosis Severity (Mean ± SD)					Spearman Correlation Coefficient	*P* Value
	No Stenosis	Mild	Moderate	Severe	*P* Value		
EFT							
LAD	8.31 ± 2.25	9.10 ± 2.37	9.93 ± 2.27	9.59 ± 2.56	0.001	0.21	0.001
LM	8.92 ± 2.39	9.31 ± 2.48	8.66 ± 2.60	11.38 ± 2.68	0.038	0.07	0.230
RCA	8.59 ± 2.31	9.21 ± 2.56	9.73 ± 2.01	9.89 ± 2.53	0.004	0.2	0.001
LCX	8.56 ± 2.32	9.23 ± 2.31	9.83 ± 2.53	9.99 ± 2.58	0.001	0.23	< 0.001
EFV							
LAD	96.7 ± 38.8	108.7 ± 44.6	133.1 ± 51.2	115.9 ± 47.7	0.001	0.19	0.002
LM	107.1 ± 43.3	113.2 ± 50.2	106.7 ± 72.3	139.7 ± 51.3	0.231	0.05	0.410
RCA	102.6 ± 42.2	106.8 ± 44.3	127.3 ± 45.1	122.9 ± 51.6	0.015	0.16	0.007
LCX	101.08 ± 40.2	114.5 ± 47.6	121.5 ± 51.7	122.3 ± 52.1	0.012	0.18	0.003

Abbreviations: EFV, Epicardial fat volume; EFT, epicardial fat thickness; LM, left main artery; LAD, left anterior descending artery; RCA, right coronary artery; LCX, left circumflex artery.

In all these models, coronary stenosis was considered as a dependent variable while, EFV, EFT and other risk factors were considered as independent variables. We assessed coronary artery involvement in two situations: first, presence or absence of stenosis; and second, presence or absence of severe stenosis. In the whole heart approach, we also considered the same groupings (presence or absence of stenosis and presence or absence of significant stenosis of at least one coronary artery in a whole heart). At first, we developed univariate logistic regression models for stenosis and significant stenosis as dependent variables [as mentioned above] in each coronary artery and the whole-heart separately based on two independent variables of EFT and EFV. The statistically significant results are presented in Table 4. Then, we implemented multivariate logistic regression models considering presence of stenosis or significant stenosis [for each coronary artery and on whole-heart basis] as dependent variables and other relevant variables [including age, gender, BMI, HTN, DM, HLP, EFT and EFV] as independent variables. For all models, the *P*-value of EFV and EFT were non-significant or the odds ratios were lower than 1.5.

Discussion

Studies have proposed that EFV is related to coronary artery stenosis and plaques as well as myocardial ischemia and acute coronary syndromes.[11-13] However, the exact mechanism involved still remains unclear. It has been suggested that epicardial fat may exert a local paracrine effect on adjacent coronary artery segments and ensuing local inflammation and changes in plaque structure.[12]

Commonly, TTE has been used to assess EFT and volume.[8] However, measurement of EAT using TTE

Table 3. Correlation Coefficients Between EFV and EFT With Single Coronary Stenosis Severity, Number of Coronary Arteries With Stenosis and Number of Coronary Arteries With Significant Stenosis

	LAD	LCX	RCA	LM	No. of Coronary Arteries With Significant Stenosis	No. of Coronary Arteries With Stenosis
EFV						
r[a]	0.189	0.178	0.164	0.050	0.130	0.178
P value	0.002	0.003	0.007	0.410	0.033	0.003
EFT						
r	0.206	0.227	0.203	0.073	0.169	0.213
P value	0.001	<0.001	0.001	0.230	0.005	<0.001

Abbreviations: EFV, epicardial fat volume; EFT, epicardial fat thickness; LM, left main artery; LAD, left anterior descending artery; RCA, right coronary artery; LCX, left circumflex artery.
[a] Pearson correlation.

Table 4. Univariate and Multivariate Logistic Regression Models for Assessment of Stenosis or Significant Stenosis in Each Coronary Arteries or Whole Heart Based on the Data of EFV or EFTY and Confounding Variables*

Dependent Variable	Independent Variable	OR in Univariate Model	*P* Value	Adjusted OR in Multivariate Model	*P* Value
Presence of LAD stenosis	EFT	1.2	<0.001	1.001	0.993
Presence of LAD stenosis	EFV	1.01	0.001	0.999	0.798
Significant LAD stenosis	EFT	1.1	0.013	1	0.997
Significant LAD stenosis	EFV	1.005	0.089	0.996	0.289
Presence of LCX stenosis	EFT	1.21	<0.001	1.04	0.562
Presence of LCX stenosis	EFV	1.009	0.002	1	0.916
Significant LCX stenosis	EFT	1.23	0.001	1.11	0.195
Significant LCX stenosis	EFV	1.008	0.014	1	0.945
Presence of RCA stenosis	EFT	1.19	0.001	0.99	0.915
Presence of RCA stenosis	EFV	1.007	0.015	0.995	0.220
Significant RCA stenosis	EFT	1.22	0.001	1.13	0.102
Significant RCA stenosis	EFV	1.009	0.004	1.005	0.219
Presence of LM stenosis	EFT	1.11	0.113	1.02	0.825
Presence of LM stenosis	EFV	1.004	0.194	1	0.980
Significant LM stenosis	EFT	1.48	0.008	1.58	0.014
Significant LM stenosis	EFV	1.013	0.056	1.016	0.080
Presence of whole heart stenosis	EFT	1.27	<0.001	1.008	0.916
Presence of whole heart stenosis	EFV	1.01	<0.001	0.998	0.685
Significant whole heart stenosis	EFT	1.14	0.012	0.994	0.932
Significant whole heart stenosis	EFV	1.005	0.065	0.996	0.298

Abbreviations: EFV, epicardial fat volume; EFT, epicardial fat thickness; LM, left main artery; LAD, left anterior descending artery; RCA, right coronary artery; LCX, left circumflex artery.
*All models are multivariate ones considering age, gender, BMI, HTN, HLP and DM as independent variables [or mediators] in addition to EFV or EFT as main under study independent variables.

has limitations. This method is highly dependent on acoustic windows and operator experience. It also has limited spatial resolution, which makes it challenging to differentiate between epicardial and pericardial fat. Moreover, the sole quantification of EFT around the right ventricular free wall can be unreliable, as the distribution of adipose tissue around the heart may not be uniform. In comparison to TTE, CTA is associated with less discomfort for the patient and is capable of providing more accurate information on EFV and thickness.

This study indicated that excessive EFV and thickness are significantly associated with higher rates of obesity and hypertension. In addition, we observed higher means of EFT and EFV in coronary arteries with more severe stenosis. However, the correlation coefficients of the arterial stenosis with EFT and EFV were weak. In addition, in all univariate models for prediction of stenosis or severe stenosis in each individual coronary artery, the odds ratios were not very considerable. The same scenario happened in multivariate analyses. Thus, although EFT and EFV are related with coronary artery stenosis, their association is not significant. Hence, although these parameters can be used as predictors for CADs, their prediction does not seem to be powerful. In this context, our findings are somehow consistent with some of the conducted studies. In a study conducted by Sarin et al, it was shown that epicardial volume measurement is an appreciable non-invasive risk factor for CAD diseases.[14] Alexopoulos et al showed that EFV is increased in the presence of obstructive CAD and can be considered as an independent predictor for non-calcified plaques.[10] Bettencourt et al investigated 215 patients with a 64 Slice-MDCT and found that EFV is related to the presence and burden of coronary atherosclerosis as an independent factor. They proposed that this relation appears to be independent from abdominal visceral fat. They also suggested that the EFV has a stronger association with CAD in comparison with abdominal visceral fat in obese patients.[15]

Oka et al suggested that high EAT volume is associated with vulnerable plaque components. They also proposed an independency between calcium score and EFV.[16] Iwasaki et al demonstrated that higher EFV was significantly related with coronary artery stenosis. However, contrary to our findings, they showed a meaningful relationship between calcium score and EFV.[17] Ito et al also demonstrated that zero calcium score cannot exclude the risk of CAD.[18]

Our study indicated a remarkable association between EFT and volume and age, male gender, BMI and hypertension. However, no considerable relation with diabetes, hyperlipidemia and Ca score was found. In studies performed by Oka et al and Dagvasumberel et al, independency of EFV and factors like diabetes and hyperlipidemia was suggested, but no remarkable relation was found between hypertension and EAT.[16,19] Bettencourt et al showed a direct relationship between epicardial fat and male sex.[15] However, Oka et al did not show a meaningful relationship between gender and EFV.[16] Dagvasumberel et al in 2012 also showed that EFV has a direct relationship with severity of coronary artery atherosclerosis in males.[19]

These differences in study outcomes could be the result of different sample size, patient population and study design. Therefore, a population-based study with a larger group of cases can be helpful to substantiate the mentioned results. Accordingly, we recommend further investigations with larger sample sizes to yield a cut off value for EFV and thickness.

The number of requested chest CTA and chest CT-scans continues to increase for diagnostic evaluation of lung and mediastinal structures. Therefore, EFV and EFT values as the potential predictor factors of CAD could be reported routinely to the referring physician.

In conclusion, in addition to the association between EFT and EFV with BMI, age, gender and hypertension, there is a weak association between these variables with the severity and presence of coronary artery stenosis as shown in univariate logistic regression models. However, they are not independent predictive factors for CAD in multivariate models consisting of other CAD risk factors. Hence, unlike previous studies, this association does not seem to be independent of other risk factors such as diabetes, hyperlipidemia and coronary artery calcium score. Therefore, as opposed to some previous studies, we suggest that EFV and thickness might be considered as weak predictors of CAD.

Authors' Contribution

All authors have contributed in this study in terms of study design, interpretation of images, data acquisition, statistical analysis, scientific writing and major revisions.

Conflict of Interest Disclosures

The authors have no conflicts of interest.

Ethical Statement

The study protocol was approved by the ethics committee of Tehran University of Medical Sciences. Written informed consent was obtained from all subjects prior to enrollment in the study.

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