Original Article

Epicardial Fat Volume Assessed by Multi-Detector Computed Tomography and Its Relationship With the Severity of Coronary Artery Disease

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ABSTRACT

Background: Epicardial adipose tissue is defined as the adipose tissue located between the outer wall of the myocardium and the visceral layer of the pericardium. Epicardial adipose tissue can be measured by echocardiography and more precisely by computed tomography (CT). The present study aimed to investigate the relationship between epicardial fat volume (EFV) assessed by multi-detector CT and the severity of coronary artery disease (CAD).

Methods: This cross-sectional study was conducted on 140 patients with a low-to-intermediate pretest probability of CAD referred for multi-detector CT coronary angiography. EFV was quantified during the non-contrast phase of the imaging protocol, and the severity of CAD was assessed in terms of segment involvement and segment stenosis scores during the contrast phase.

Results: The study population included 105 men (75%) at a mean age of 56±10.27 years. Risk factors of atherosclerosis were analyzed among the patients. Body mass index ranged between 24 kg/m^2 and 30.9 kg/m^2, hypertension was detected in 77.5%, diabetes mellitus was reported in 55%, and 67.5% were smokers. While 17.5% of the studied patients had normal coronaries, 37.5% had single-vessel disease and 45% had multi-vessel disease. A significant relationship existed between EFV and the coronary artery calcium score (P=0.011). Highly significant relationships were also detected between EFV and both segment involvement and segment stenosis scores (P=0.001 and P=0.003, respectively). Patients with normal coronary arteries had a lower EFV than those with coronary lesions (a highly significant relationship, P=0.004), whether with single-vessel or with multi-vessel disease.

Conclusions: EFV increased in patients with either significant coronary artery stenosis or coronary calcification. Risk factors of atherosclerosis showed direct relationships with EFV. ***(Iranian Heart Journal 2021; 22(4): 54-65)***

KEYWORDS: EFV, CAD, SIS score, SSS score

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The distribution of body fat varies among individuals and may be as important as the amount of body fat in determining risk. An excess accumulation of fat around the upper body is associated with a higher risk of coronary artery disease (CAD) regardless of total body fat. [1]
Epicardial fat, defined as the adipose tissue located between the outer wall of the myocardium and the visceral layer of the pericardium, surrounds the heart and the coronary vessels. The blood supply of epicardial fat is small myocardial coronary arteries. [2]
The thickness of epicardial fat around the right ventricle is normally less than 7 mm in healthy lean individuals. Fat volume around the heart correlates with advancing age, and it is larger in males. Ethnicity is another influencing factor since adipose tissue is larger in Caucasians, followed by Asians, blacks, and Hispanics. [2]
Fat around vessels and the heart may have a supportive mechanical purpose, attenuating vascular tension and torsion and participating in vessel remodeling. The rates of fatty acid incorporation and release are higher in cardiac than in other adipose depots, and lipogenesis is stimulated by insulin only in this fat depot. Cardiac and perivascular adipose tissues may act as a local energy provider and a buffer against toxic levels of free fatty acids in the myocardium and the arterial circulation. Epicardial fat is a white adipose tissue storage fat that covers 80% of the heart's surface, representing 20% of the organ's total weight. Therefore, epicardial fat is considered to be a real visceral adipose tissue. [2-3]
Epicardial adipose tissue is mainly present in the atrioventricular and interventricular grooves, following the course of the main coronary vessels, and over the free wall of the right ventricle and the left ventricular apex. [3] Epicardial adipose tissue is closely related to the adventitia of the coronary arteries without a barrier. This tissue secretes several pro-atherogenic mediators (eg, adipokine, adiponectin, resistin, and inflammatory cytokines) that may directly influence the development and progression of atherosclerosis and CAD through local paracrine and endocrine effects. Previous studies have suggested that fat deposition in visceral organs and epicardial tissue may be related to metabolic risk factors and a predictor of the severity of CAD and the extent of coronary artery atherosclerosis. [4-5]
The thickness of epicardial adipose tissue can be considered a potential risk factor in the early phases of coronary plaque formation and progression besides its impact on plaque vulnerability. Plaque rupture arises in the fibrous layer, which is thin and heavily infested by macrophages, which are responsible for maintaining the proinflammatory state. Furthermore, epicardial adipose tissue secretes mediators such as the tumor necrosis factor and interleukin 1 that stimulate macrophages and induce the apoptosis of vascular smooth muscles and, thus, contribute to vascular remodeling and plaque rupture. [6, 7]
Therapeutic interventions in epicardial adipose tissue have been previously investigated. In a previous investigation, a 3-month intense exercise program was applied on obese men; and surprisingly, a greater magnitude of reduction in adipose tissue was witnessed in epicardial fat than in the waist and body mass index (BMI). These changes matched significant improvements in systolic blood pressure and insulin sensitivity. [8]
Epicardial adipose tissue can be measured with echocardiography against the right ventricular free wall. Other modalities include magnetic resonance imaging and multi-detector computed tomography (MDCT). MDCT has emerged as a reference tool to assess pericardial thickness and evaluate pericardial fat volume, besides its role in the measurement of the coronary

calcium score and the diagnosis of obstructive CAD. [9, 11]

The present study aimed to evaluate the relationship between epicardial fat volume (EFV) assessed by MDCT and the severity of CAD.

METHODS

The present cross-sectional study was conducted on 140 consecutive patients referred to our center for MDCT angiography. Written informed consent was obtained from all the subjects.

The study included all patients presenting with chest pain with a low-to-intermediate pretest probability of CAD according to the Diamond and Forrester Pretest Probability of Coronary Artery Disease. [10] Patients were excluded if they had renal insufficiency (serum creatinine >1.5 mg/dL), a previous history of percutaneous coronary intervention or coronary artery bypass grafting, a recent myocardial infarction, dye allergies, irregular heart rhythms like atrial fibrillation and frequent extrasystoles, difficulties in undergoing CT (eg, inadequate breath-holding and heart failure), having acute coronary syndromes (ie, elevated cardiac biomarkers and/or dynamic electrocardiographic [ECG] changes), and a high probability CAD.

All patients had a comprehensive history taking; complete clinical examinations including BMI measurement and ECG; and routine laboratory investigations including random blood glucose levels, serum creatinine levels, and complete lipid profiles. Additionally, MDCT was done for all the subjects with a Toshiba Aquilion One 320-slice CT scanner.

Patient Preparation and Techniques

Heart rate was assessed for all the patients 60 minutes before scheduled CT examinations; and if heart rate exceeded 75 bpm, the patient was given oral beta-blockers or calcium channel blockers. The sublingual dose of nitroglycerin (5 mg) was administered just before the scan examinations. All the scans were preceded by non–contrast-enhanced scanning for coronary calcium scoring. All the patients received an intravenous nonionic iso-osmolar contrast medium (via the test bolus technique) and a bolus of 10 mL of the contrast agent injected intravenously (rate =5 mL/s) through an 18–20 G intravenous cannula, followed by a saline flush (20 mL). Then angiography was done through the injection of 60 mL of the same contrast agent (rate =6 mL/s) using a power injector. After the accurate calculation of the delay and checking the ECG trigger, image acquisition was started from the tracheal bifurcation (above the origin of the coronary arteries) and ended at the dome of the diaphragm. The image data sets were analyzed by means of 2D, multiplanar reformatted images (vertical, long-axis, and short-axis views), curved multiplanar reformatted images, maximum-intensity projection images, and volume-rendered images to show the walls and lumens of the vessels and all the surrounding tissue and assess the patency of the vessels. The images were interpreted by 2 independent experts, who were blinded to the patients' clinical data.

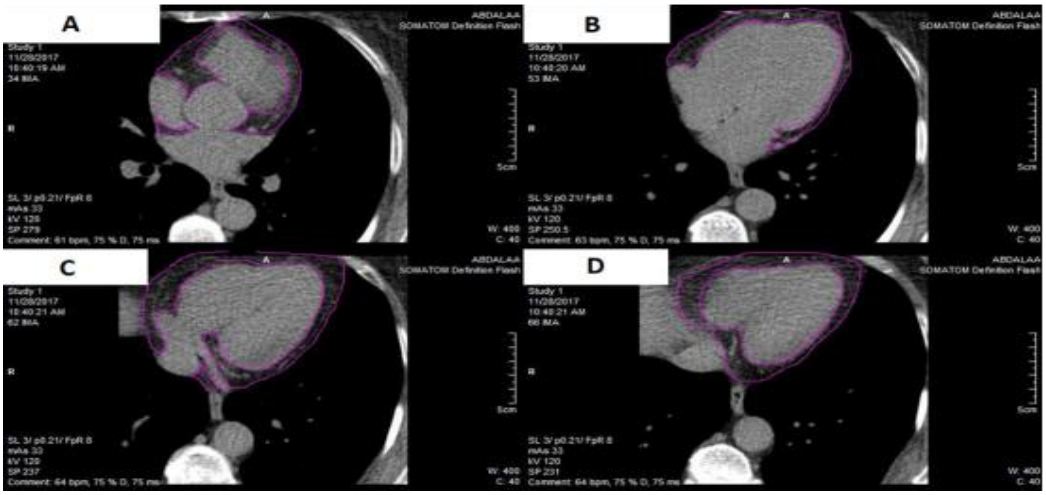
Coronary segments were visually scored for the presence of coronary plaques in terms of the segment involvement score (SIS), which classifies the coronary artery tree into 16 segments according to the American Heart Association classification. Additionally, *t*he segment stenosis score (SSS) was calculated as a measurement of the total coronary plaque burden. Each segment was given a score from 0 to 3: 0 for normal, 1 for mild (<50%), 2 for moderate (50%–69%), and 3 for severe (≥70%) according to the degree of lumen stenosis. The summation of all segment scores gives an entire score ranging from 0 to 48. (A score >5 points was defined

as high-risk). [11] Coronary calcium scoring was used to measure the amount of the calcium deposit in the coronary arteries by the Agatston score. [12]

Epicardial fat was quantified via a semi-automated technique (Vitrea workstation) for measuring the amount of fat. Epicardial fat was visualized from the origin of the left main coronary artery to the cardiac apex (just below the posterior descending artery). EFV was measured using 3.0 mm thick axial slices for calcium scoring. We manually traced the parietal pericardium in every slice starting from the aortic root to the apex. The computer software then automatically interpolated and traced the parietal pericardium in all the slices interposed between the manually traced slices to measure EFV in cm^3 as is shown in Patient IV (Fig. 1). Fat voxels were identified using threshold attenuation values of −30 to −250 HU. The upper limit of normal EFV determined by tomography indexed to body surface area was 68.1 cm^3/m^2. Further, the number of the segments affected was determined in terms of the SIS score, and the degrees of lesions were determined in terms of the SSS score. [13]

Statistical Analysis

Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS), version 20. Continuous variables were presented as the mean ± the standard deviation (SD). Categorical variables were expressed as numbers and percentages. The Kolmogorov–Smirnov test for normal distribution was used to differentiate between parametric data and nonparametric data. The ANOVA test was also applied to assess the relationship between different variables. Univariate and multivariate analyses were conducted. A receiver operating characteristic (ROC) analysis was done to determine the optimal cutoff value of EFV for the presence of CAD and obstructive CAD. The area under the curve (AUC), sensitivity, and specificity were calculated to analyze the diagnostic accuracy. For all the statistical tests, a *P*-value of less than 0.05 was taken to indicate a significant difference.



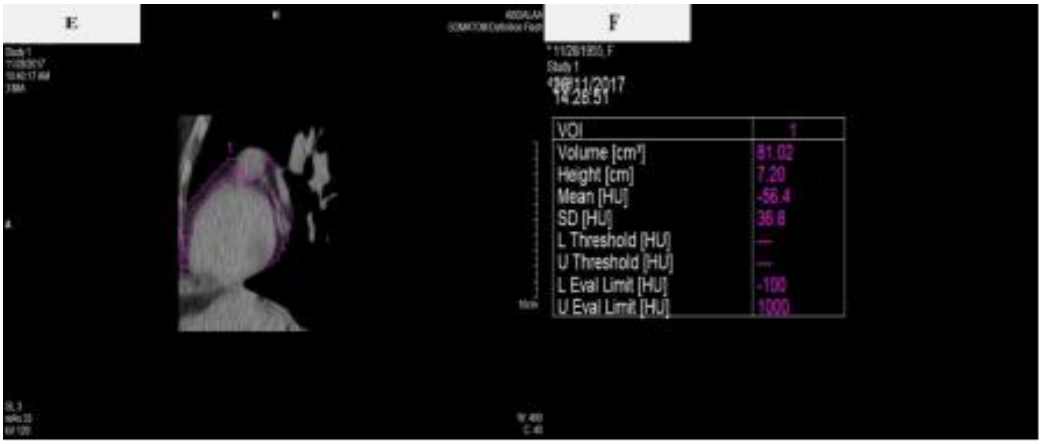


Figure 1. The image depicts the measurement of epicardial fat volume (EFV) by computed tomography. The area of interest is defined by the manual delineation of the epicardial fat, and the volume is calculated (81.02 cm^3) in a semi-automatic way by specific software as is shown in slide F.

RESULTS

This study included 140 patients, of whom 60 patients were excluded. Sixteen patients were excluded due to high serum creatinine, 12 due to irregular heart rhythms, 15 due to inadequate breath-holding, and 17 due to acute coronary syndromes. Thus, the study was conducted on 80 patients. Men comprised 75% of the studied population. The mean age was 56±10 years.

Regarding the demographic characteristics of the studied patients, BMI ranged between 24 kg/m^2 and 30.9 kg/m^2, 62 patients suffered from hypertension, 44 patients had diabetes mellitus, 54 were active smokers, 28 had a family history of premature CAD, 10 had peripheral vascular diseases, and 2 had a previous history of cerebrovascular strokes.

The severity and extent of CAD were assessed by variable scores. The coronary artery calcium (CAC) score, which determines the degree of the calcification of coronary plaques, ranged between 0 and 1866, with a mean value of 207.11±397.8 according to the Agatston score. The SIS score, which determines the number of segments involved, ranged between 0 and 7, with a mean of 1.85±1.64. The SSS score, which assesses the degree of the severity of CAD, ranged between 0 and 20, with a mean of 5.05±4.59. EFV ranged between 58 cm^3 and 225 cm^3, with a mean of 132.7±39.11 cm^3 (Table 1).

Table 1. Different scores assessing the severity of coronary atherosclerosis

	Mean ± SD	Range	Median	IQR
Calcium score	207.11±397.8	0-1866	45.2	0- 301.05
SIS score (16)	1.85±1.64	0-7	1	1-3
SSS score (48)	5.05±4.59	0-20	3	2-8.75
EFV (cm^3)	132.7±39.11	58-225	130.2	103.7-156.3

SIS, Segment involvement score; SSS, Segment stenosis score; EFV, Epicardial fat volume

Regarding the relationship between EFV and risk factors for atherosclerosis, EFV showed highly significant associations with BMI, hypertension, and diabetes mellitus (P=0.001, P=0.002, and P=0.002, respectively). Nonetheless, EFV had no significant associations with smoking, a family history of CAD, and cerebrovascular diseases (Table 2).

Table 2. Relationships between EFV and risk factors for atherosclerosis

		Mean ± SD	Range	Median	IQR	*P*-value
Age Group	<60 y	126.19±37.63	58-211.7	124.45	99.7-141.7	0.15
	>60 y	144.79±40.55	85-225	140.5	170.7	
Body Mass Index	<25	90.38±23.48	58-139	87	78.2-99.7	0.001
	>25	143.28±35.08	85-225	134.5	122.2-159.5	
Sex	Male	135.87±38.08	78-225	132	104-157.2	0.38
	Female	123.2±43.16	58-196	117.5	89.2-150.5	
Diabetes Mellitus	No	125.2±47.19	78-225	130.5	91.5-150	0.002
	Yes	138.7±40.59	58-212	130	116.7-169.2	
Hypertension	No	101.78±27.45	78-164	93	82-114	0.002
	Yes	141.68±37.77	58-225	135	122-158	
Smoking	No	118.38±29.90	87-185	111	91.5-138.5	0.11
	Yes	139.59±41.71	58-225	134	121-160	
Family History of CAD	Negative	130.54±43.94	58-225	124.5	92.2-157.2	0.64
	Positive	136.71±29.94	78-196	133	122.5-145.2	
Previous PVD	No	128.77±39.62	58-225	125	102-150	0.11
	Yes	160.2±23.54	132-196	160	140.5-180	
Previous Stroke	No	133±39.66	58-225	132	104-157	0.76
	Yes (n=1)	121±0	121-121	121	121-121	

EFV, Epicardial fat volume; CAD, Coronary artery disease; PVD, Peripheral vascular disease

EFV showed highly significant positive associations with total serum cholesterol, serum low-density lipoprotein, and serum triglycerides, whereas it had significant inverse associations with serum high-density lipoprotein (Table 3 & and Fig. 2).

Table 3. Relationships between epicardial fat volume and dyslipidemia

Risk Factors	*r*	*P*-value
Total cholesterol	0.518	0.001
Epicardial fat volume	0.604	0.001
Triglycerides	0.366	0.020
High-density lipoprotein	-0.480	0.020

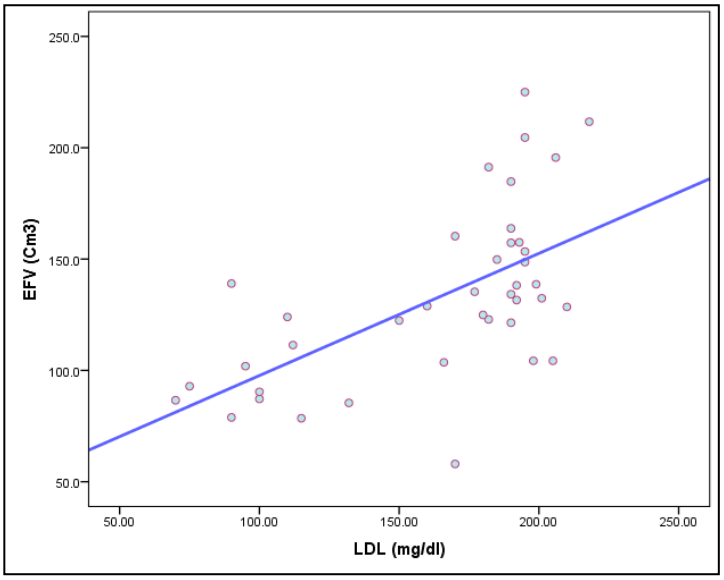


Figure 2. The image illustrates the scatter plot of the correlation between low-density lipoprotein (LDL) and epicardial fat volume (EFV).

Vis-à-vis the extent of atherosclerosis as assessed by CAC, SSS, and SIS scores, highly significant positive correlations were detected between EFV and CAC, SSS, and SIS scores (*P*=0.01, *P*=0.03, and *P*=0.001, respectively) (Table 4).

Table 4. Correlations between the extent of atherosclerosis and EFV

Scores	EFV	
	r	*P*-value
CAC	0.397	0.01
SSS (16)	0.459	0.03
SIS (48)	0.518	0.001

EFV, Epicardial fat volume; SIS, Segment involvement score; SSS, Segment stenosis score; CAC, Coronary artery calcium score

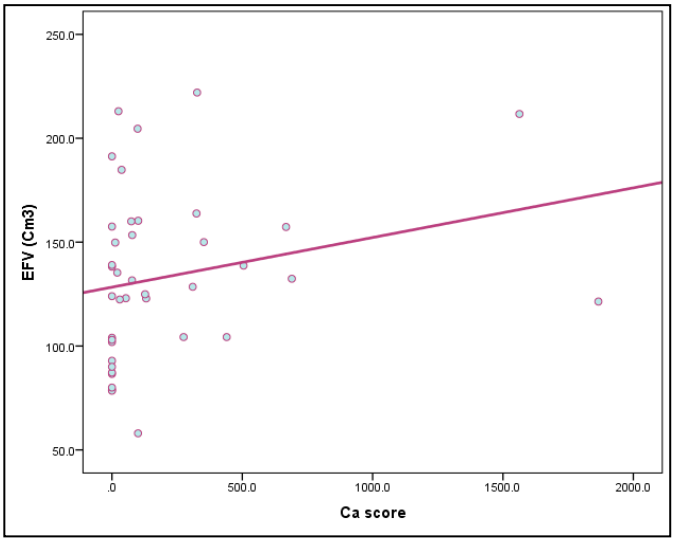


Figure 3. The image demonstrates the scatter plot of the correlation between the coronary artery calcium score (CAC) and epicardial fat volume (EFV).

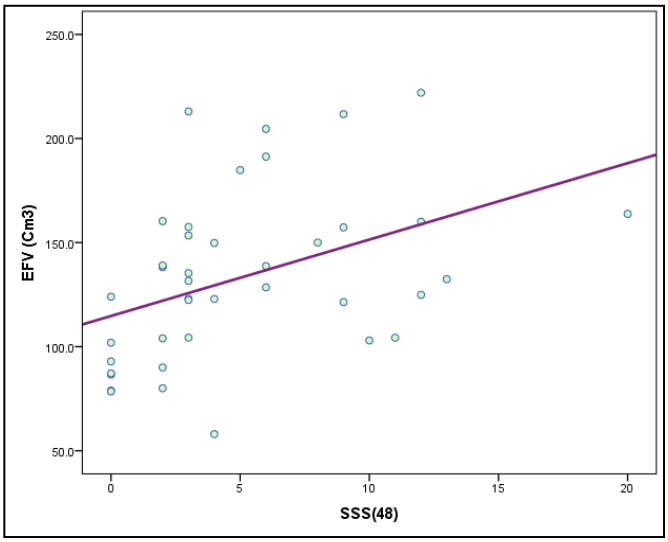


Figure 4. The image shows the scatter plot of the correlation between the segment stenosis score (SSS) and epicardial fat volume (EFV).

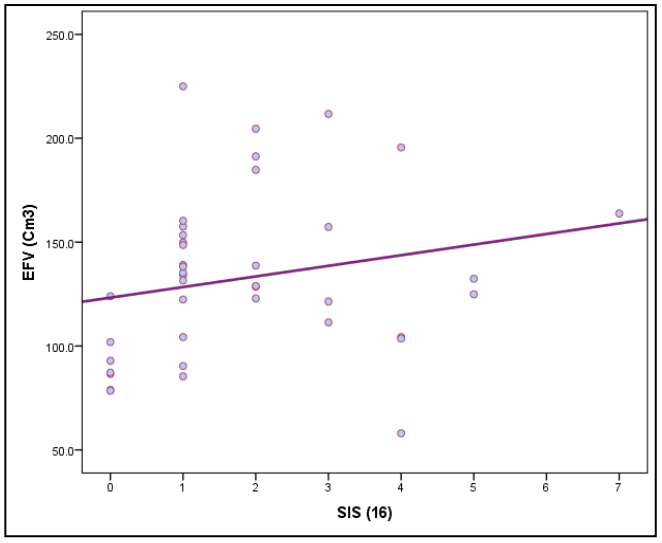


Figure 5. The image depicts the scatter plot of the correlation between the segment involvement score (SIS) and epicardial fat volume (EFV).

The SSS score assesses the severity of CAD, with values above 5 denoting high-risk patients. EFV showed a highly significant correlation with the SSS score (*P*=0.009) (Table 5).

Table 5. Correlation between the SSS score and EFV

EFV	SSS<5	SSS>5	*P*-value
Mean ±SD	120.7±36.7	154.2±38.1	0.009
Median (IQR)	122.9(88.6-144.4)	150(124.9-191.3)	
Range	58-213	103-222	

SIS, Segment involvement score; EFV, Epicardial fat volume

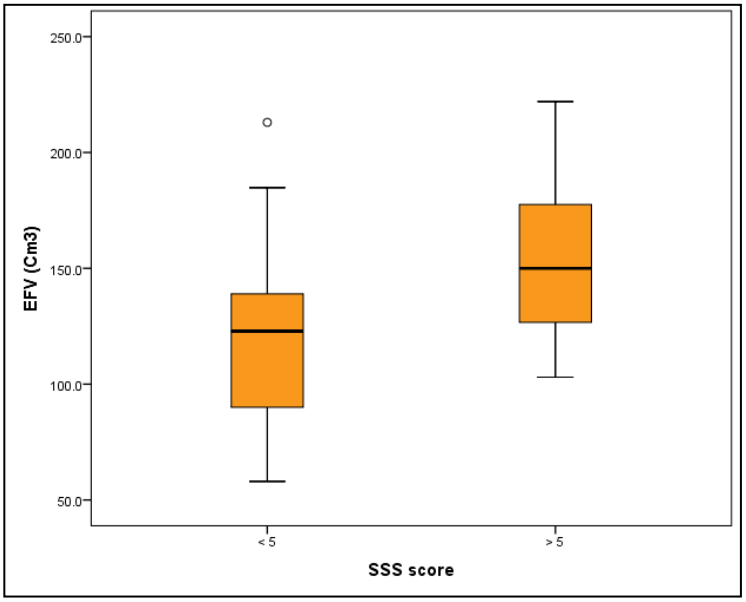


Figure 6. The image illustrates the box plot of the correlation between the segment involvement score (SSS) and epicardial fat volume (EFV).

This study was performed on 80 patients. Out of this total, 17.5% had normal coronaries, while 37.5% had single-vessel and 45% had multi-vessel diseases. Patients with normal coronary arteries had lower EFV than those with coronary lesions (a highly significant relationship, *P*=0.004), whether with single-vessel or with multi-vessel disease. (Table 6). Nevertheless, EFV exerted no significant impact on the number of affected coronaries.

Table 6. Correlation between EFV and the SIS score

	SIS Score			
	Normal Coronaries	Single-Vessel Disease	Multi-Vessel Disease	*P*-value
N	14	30	36	
EFV (cm^3) Mean±SD	92.85±15.93	150.04±36.59	133.82±38.15	All: 0.001 Normal & Single: 0.001 Normal & multiple: 0.011 Single & multiple: 0.187
Range	78.5-124	90.4-225	58-211.7	
Median (IQR)	87.2 (78.8-101.9)	148.6 (131.6-160.3)	128.7 (109.6-158.9)	

EFV, Epicardial fat volume; SIS, Segment involvement score

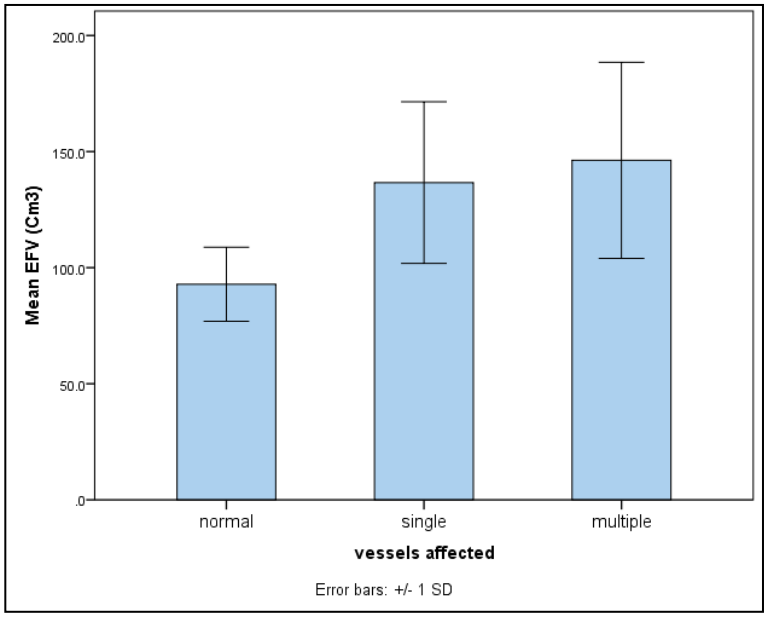


Figure 7. The image depicts epicardial fat volume (EFV) among the affected vessels as assessed by the segment involvement score (SIS) score.

DISCUSSION

Epicardial adipose tissue can affect the development and progress of coronary atherosclerosis through multifactorial mechanisms that can be summarized in lipotoxicity, glucotoxicity, innate immunity, and oxidative stress. Epicardial fat is a part of total body adipose tissue and is strongly influenced by atherosclerotic risk factors. The quantification of either the thickness or the volume of epicardial fat can be accurately achieved using MDCT.

This study aimed to investigate the relationship between EFV and risk factors for atherosclerosis, as well as the severity of coronary atherosclerosis as assessed by CAC, SSS, and SIS scores. Our study, conducted in Nasr City Police Hospital,

recruited 80 consecutive and eligible patients referred for CT coronary angiography. The mean age of the studied population was 56±10.27 years, with a male predominance. The entire studied group presented with chest pain with a low-to-intermediate pretest probability for CAD.

In this study, risk factors of atherosclerosis, including obesity, diabetes mellitus, hypertension, and dyslipidemia were significantly associated with increased EFV. The association between EFV and dyslipidemia was more pronounced concerning increased low-density lipoprotein cholesterol, decreased high-density lipoprotein cholesterol, and elevated total cholesterol levels. A similar association was reported by Akyol et al, [14] who observed a close relationship in teenagers with obesity and metabolic syndromes between epicardial adipose tissue, the thickness of the carotid intima, and early cardiac dysfunction parameters, showing the predictive role of lipid accumulation in adult and elderly populations. Similarly, Mohammadzadeh et al [15] showed that increased EFV was associated with CAD, age, BMI, and hypertension.

In this study, we assessed the severity and extent of coronary atherosclerosis using different scores (viz, SIS, SSS, and CAC scores). Our results showed that EFV was significantly associated with coronary atherosclerosis, calcification, and coronary artery stenosis. Larger EFV showed ascending trends with a higher CAC score, and a worse SSS score denoted more intense CAD.

Yadav et al [16] studied the correlation between quantified epicardial fat and the severity of CAD by using CT and found higher EFV in patients with a greater degree of coronary artery stenosis. Mahabadi et al [17] sought to determine whether EFV could predict coronary events in the general population by MSCT. They assessed multivariable associations between epicardial adipose tissue and cardiovascular risk factors, the CAC score, and coronary events with the aid of regression analysis. Out of 4093 participants, 130 subjects developed a fatal or nonfatal coronary event; hence, Mahabadi and colleagues concluded that epicardial fat was associated with fatal and nonfatal coronary events in the general population independent of traditional cardiovascular risk factors. This finding is in agreement with our study insofar as we showed that EFV was significantly associated with both coronary atherosclerosis and coronary artery stenosis, leading to hazardous cardiovascular events. Nonetheless, in our study, MDCT was conducted on patients with suspected CAD not on the general population.

Okada et al [18] analyzed the relationship between the volume of epicardial adipose tissue and the severity of CAD by MDCT in nonobese patients, in conjunction with the potential effects of epicardial fat on coronary plaque morphology or extension. They concluded that individuals with increased EFV had more severe coronary plaques, which were not essentially calcified, denoting that the thickness storage of epicardial fat played a key role in the progression of coronary artery atherosclerosis. In addition, correlations between increased epicardial adipose tissue and reduced high-density lipoprotein cholesterol, increased interleukin-6, and elevated high-sensitivity C-reactive protein were observed. In our study, elevated high-density lipoprotein cholesterol was a significant risk factor, and EFV was inversely proportional to its increase.

Abazid et al [19] investigated the association between the volume of epicardial adipose tissue and subclinical CAD defined by a high CAC score, using CT in patients with a mild-to-moderate risk for CAD. Patients with CAC had significantly higher EFV than those without a high CAC score. Both the

quality and quantity of epicardial adipose tissue, derived from non-contrast CT scans, predicted subclinical CAD. A higher volume of epicardial fat was associated with a higher CAC score Additionally, Ito et al [20] reported a strong positive correlation between EFV and the coronary plaque burden even in the absence of extensive coronary calcification.

CONCLUSIONS

The results of the current study showed that EFV had a positive association with coronary calcification and the severity of coronary atherosclerosis, besides its positive relationship with risk factors for atherosclerosis.

Limitations

The single-center design of the present study and its relatively small cohort of patients are its salient limitations.

Declarations:

Ethical approval and consent to participate

The Research Ethics Committee of the Faculty of Medicine, Ain Shams University, has reviewed and approved the study (FMASU M S 71/2020).

The Research Ethics Committee (REC) of the Faculty of Medicine, Ain Shams University, operates according to the guidelines of the International Council of Harmonization (ICH) Anesthesiology and the Islamic Organization of Medical Science (IOMS), the United States Office of Human Research Protection, and the United States code of federal regulations. It also operates under federal wide assurance (FWA 000017585). The REC does not declare the name of its members according to the university and REC standard operating procedures. The data of the recruited patients were presented after the subjects received comprehensive information about all the steps of the study and after they provided written informed consent on condition of the protection of privacy and confidentiality.

Consent for Publication:

Not applicable.

Availability of Data and Material

All data, including angiogram films and stored echocardiographic loops, are available in Ain Shams University's Cath Lab and Echocardiography Archives.

Conflict of Interest

All the authors declare that there are no conflicts of interest.

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The study received no funding. The studied cohort was recruited from a pool of patients referred to Ain Shams University's Cardiology Department, Cath Lab, and Echocardiography Unit.

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Not applicable.

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