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***Case Control Study***

**Quantification of epicardial fat: Which method can predict significant coronary artery disease?**

Saad Z *et al*. Best method for epicardial fat quantification

Zizi Saad, Mohamed El-Rawy, Ragab H Donkol, Sami Boghattas

**Zizi Saad, Mohamed El-Rawy,** Cardiology Department, Aseer Central Hospital, Abha, Saudi Arabia and Faculty of Medicine, Zagazig University, Ash Sharqia Governorate 44516, Egypt

**Ragab H Donkol,** Radiology Department, Aseer Central Hospital, Abha, Saudi Arabia and Faculty of Medicine, Cairo University, Giza 12411, Egypt

**Sami Boghattas,** Radiology Department, Aseer Central Hospital, Abha 61321 Saudi Arabia

**Author contributions:** Saad Z and Donkol RH designed the study, performed CCTA studies, and wrote the manuscript; Alrawy M and Donkol RH shared selection of cases, clinical and echocardiographic assessment as well as collection of data and interpreted CCTA scans; BoghattasS analyzed the data**.**

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**Correspondence to:** **Ragab H Donkol, MD,** Department of Radiology, Faculty of Medicine, Cairo University and Assir Central Hospital, PO Box 34, Abha 61321, Saudi Arabia. ragabhani@hotmail.com

**Telephone**: +966­7­2291169

**Fax**: +966­3­8552244

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**Abstract**

**AIM**: To compare the predictive value of three methods of epicardial fat (EF) assessment for presence of significant coronary artery disease (CAD) [*i.e.,* epicardial fat volume (EFV), EFV indexed with body surface area (EFV/BSA) and EFV indexed with body mass index (EFV/BMI)].

**METHODS**: The study was performed on 170 patients (85 women and 85 men) with clinical suspicion of CAD. They aged 26-89 years with a median age of 54 years. The patients were classified into three groups: Group 1: 58 patients with normal coronary arteries; group 2:48 patients with non-significant CAD and group 3: 64 patients with significant CAD. The three methods for assessment of epicardial fat were retrospectively studied to determine the best method to predict the presence of significant CAD.

**RESULTS**: The three methods for epicardial fat quantification and measurements, *i.e.,* EFV, EFV/BSA and EFV/BMI with post- hoc analysis showed a significant difference between patients with significant coronary artery disease compared to the normal group. Receiver operating characteristic curve analysis showed no significant difference between the three methods of epicardial fat measurements, the area under curve ranging between 0.6 and 0.62. The optimal cut-off was 80.3 cm3 for EFV, 2.4 cm3/m2 for EFV indexed with BMI and 41.7 cm3/ (kg/m2) for EFV indexed with BSA. For this cut-off the sensitivity ranged between 0.92 and 0.94, while specificity varied from 0.31 to 0.35.

**CONCLUSION**: Any one of the three methods for assessment of epicardial fat can be used to predict significant CAD since all have the same equivalent predictive value.

**Key words:** Epicardial fat volume; Quantification of epicardial fat; Coronary heart disease

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**Core tip:** There is a great correlation between the volume of epicardial fat and presence of significant coronary artery disease. There are different methods for quantification of epicardial fat volume. The aim of the study is to compare the predictive value of the three methods used for quantification of epicardial fat [epicardial fat volume (EFV), EFV indexed with body surface area and EFV indexed with body mass index] for presence of significant coronary artery disease. The study concluded the three methods for assessment of epicardial fat have the same equivalent predictive value for significant coronary artery disease and any one of them can be used as a sensitive predictor for significant coronary artery disease.

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**INTRODUCTION**

Epicardial fat (EF) is the visceral fat of the heart deposited under the visceral layer of the pericardium. Under normal physiological conditions, EF tissue displays biochemical, mechanical and thermogenic cardioprotective properties. Under pathological circumstances, EF can be strongly related to the development of coronary artery disease (CAD). The accumulation of EF is known to be a rich source of free fatty acids and a number of proinflammatory cytokines[1-3].

It has been hypothesized that EF may act as a paracrine (immunological) organ that influences the coronary arteries by promoting chronic inflammation and endothelial dysfunction[4-6].

Several imaging modalities can be used to quantify EF volume (EFV) such as echocardiography, computed tomography, and magnetic resonance imaging[7]. Due to distinct low attenuation values of fat on computed tomography (CT). ECG-gated cardiac CT with its high spatial resolution and true volume coverage of the heart, allows accurate measurement of epicardial and thoracic fat distances and volumes[6,7].

Besides EFV, some authors derived a second parameter, the body surface area indexed EFV (EFV/BSA)[8,9]; however, comparison between these two parameters has not been considered. Moreover, despite the predictive value of higher body mass index for cardiovascular event[10,11], the added value of body mass index (BMI)-adjusted EFV (EFV/BMI) also has not been previously assessed as well.

The aim of the current study is to compare the predictive value of the three methods for EF assessment (EFV, EFV/BSA and EFV/BMI) for presence of significant CAD.

**MATERIAL AND METHODS**

***Patients***

A total of 170 consecutive patients with clinical suspicion of coronary artery disease (CAD) aged 26-89 years with a median age of 54 years (85 women and 85 men) were included in our study From November 2012 through February 2014. Patients underwent 128-MDCT according to appropriate use criteria for cardiac computed tomography[12]. All participants provided written informed consent and the study was approved by institutional ethics committee.

 The patients were divided into 3 groups according to the severity of coronary artery stenosis assessed by quantitative coronary angiography. Patients in group1 have normal coronary arteries. Patients in groups 2 were have non-significant coronary artery stenosis with percent-diameter stenosis less than 50%. Patients in groups 3 have significant CAD with percent-diameter stenosis more than 50% or occlusion[13].

***Multidetector computed tomography***

Our patients were scanned with a 128-multidetector computed tomography (MDCT) dual source scanner (SOMATOM Flash; Siemens Medical Solutions, Erlangen, Germany). Patients with uncontrolled heart rate (> 65 beats per minute) received oral beta blocker (metoprolol 50 mg) before the CT scan. Sublingual nitroglycerin 0.5 mg was administrated before the scan to achieve coronary vasodilation. A non-contrast CT scan was performed to determine the total calcium burden of the coronary tree (sequential scan with 32 Å~ 0.6-mm collimation, tube current 60 mA at 120 kV). Contrast-enhanced CT angiography data were acquired with the use of a spiral scan with 32 Å~ 0.6-mm collimation, 330-ms gantry rotation, pitch of 0.2, and tube voltage at 120 kV.

Sequential ECG-triggering scans were performed in 142 patients with controlled heart rate and retrospective ECG-gating scans with tube current modulation were performed in 28 patients due to heart rate variability. Intravenous contrast agent (60-90 mL; 350 mg iodine/mL) was injected with flow rate of 5.0 mL/second followed by a 30-mL saline chaser[1].

**Image interpretation:** The total calcium score was calculated and interpretation of CCTA was analysed for all patients using commercially available software packages “Syngo Via”, Siemens Healthcare, Forchheim, Germany).

***Measurement of EFV***

EFV was measured blindly by two observers for all patients using an offline workstation (Aquarius NetStation; TeraRecon Inc., San Mateo, CA). Using the 3.0-mm-thick axial slices used for calcium scoring, the parietal pericardium was traced manually in every 4th slice starting from the aortic root to the cardiac apex[1] (Figure 1). The computer software then automatically interpolated and traced the parietal pericardium in all slices interposed between the manually traced slices. The automatically traced slices were examined and verified for accuracy. Fat voxels were identified using threshold attenuation values of -30 to -190 HU (Figure 2).

Division the estimated EFV of every patient by patient’s BSA calculated the indexed EFV to BSA (EFV/BSA). Also, division of EFV by patient’s BMI calculated the indexed EFV to BMI (EFVB/MI).

***Statistical analysis***

The statistical analysis was performed by StatDirect 2.8.0 and Mecalc 9.2.1.0 (for ROC curve analysis and comparison). Because the analyzed quantitative variables (EFV, EFV/BMI, EFV/BSA, BMI, BSA and age) were not normally distributed (Shapiro and Wilk test), the values are expressed as medians with interquartile range. Dichotomous data are presented as frequency (percent).

Differences in characteristics of patients were compared using Pearson's chi-square test for dichotomous variables (or Fisher's exact test when appropriate) and Kruskall-Wallis test for continuous test.

To compare the predictive performance for risk of significant CAD between the three EF parameters, we plotted receiver operating characteristic (ROC) curve from which the optimal cutoff was derived and we calculated the area under curve (AUC). AUC, optimal cutoff, sensitivity and specificity for each EFP and pairwise comparison of AUC have been determined. A two-tailed *P*-value less than 0.05 were considered as statistically signiﬁcant; significant differences are presented with asterisk in the tables. The statistical methods of this study were reviewed by a biostatistician.

**RESULTS**

***General characteristics***

Table 1 illustrated the important clinical findings and measurements of the patients among the three groups of patients.

***Correlation of EFP with CT coronary angiography results***

Comparison of EF parameters with CT coronary angiography results is presented in Table 2. Comparison of EFP medians revealed a progressive increase from group 1 to group 3. The medians where 81, 104 and 113 for EFV (cm3), 2.7, 3.7 and 3.8 for EVV/BMI (cm3/m2) and 45.6, 53.9 and 61.8 for EFV/BSA [cm3/(kg/m2)]. Nevertheless, the post- hoc analysis showed significant difference only between groups 1 and group 3 for all EFP: *P* = 0.002 for EFV, *P* = 0.012 for EFVBMI, and *P* = 0.007 for EFVBSA.

***ROC curves analysis***

ROC curve for the three the EFP is presented in Figure 3. AUC was 0.62 for EFV, 0.6 for EFVBMI and 0.61 for EFVBSA and pairwise comparison failed to show significant difference. The optimal cut-off was 80.3 cm3 for EFV, 2.4 cm3/m2 for EFVBMI and 41.7 cm3/(kg/m2) for EFVBSA. Sensitivity and specificity were respectively 0.92 and 0.35 for EFV, 0.93 and 0.31 for EFVBMI, and 0.94 and 0.32 for EFVBSA.

**DISCUSSION**

Noninvasive quantitative measurement of epicardial fat volume from CT is feasible, and may play a clinical role in cardiovascular risk assessment[6]. It have shown its reproducibility and correlation to CAD presence, severity, and prognosis[14-16].

 Recently, multiple studies have shown a deleterious relationship between epicardial fat burden and coronary atherosclerosis, arrhythmogenesis and major adverse cardiovascular events (MACE)[17,18]. In this study, the epicardial fat volume is correlated with the presence of coronary artery stenosis. In agreement with this findings, Alexopoulos *et al*[19] observed on coronary CT angiography a significant increase in epicardial fat volume with increasing coronary luminal stenosis; epicardial fat volume was also larger in patients with mixed or noncalcified plaques.

A recent study by Nakazato *et al*[20]assessed the relationship of epicardial fat volume to weight, BMI and waist circumference, and evaluated whether changes in these parameters over a 4-year period influenced epicardial fat volume measured by noncontrast CT in a relatively healthy asymptomatic population. They found that weight, BMI and waist circumference demonstrated moderate cross-sectional relationships to epicardial fat volume, and that changes in these parameters were related to epicardial fat volume change

In another study, Shmilovich *et al*[9] assessed the body surface area indexed EVF in a healthy population and validated it as a predictor of major adverse cardiovascular events.

By reviewing the literature, the two parameters EFV and EFV/BSA, have no clear evidence of differences in their accuracies and predictive values[9,18-20]. In the current study we compared the predictive value of three EFP for the presence of significant CAD. To our knowledge, no similar studies have been performed before and EFV/BMI has not previously assessed also, the predictive value of EF/VBSA for CAD has not been compared with EFV.

 The major outcome of the present study, derived from the ROC curve analysis, is that the three methods for assessing the EF have an equivalent predictive value for significant CAD and any one of them can be used as a predictor for significant CAD. Therefore, the clinical impact of the indexed EFV seems to be limited. To note that in the series using the indexed EFV to BSA, the benefit of such indexing has not been evaluated and ROC curve analysis has not been applied for assessment of possible increase in the predictive value for total occlusion of coronary arteries[16] or major adverse cardiovascular events[9].

 According to the traditional academic point system, the accuracies of the three methods for measuring EF are classified as poor considering that the AUC are in the range 0.6-0.7. This limited accuracy is related mainly to the low specificity, ranging from 0.31 to 0.35, while the sensitivity is high, varying from 0.92 to 0.94, therefore the three methods can be considered as sensitive but poorly specific predictors for significant CAD. Consequently, indexing EFV by BSA or BMI doesn’t improve significantly the sensitivity and, more importantly, the specificity of EF for significant CAD.

 In the current study, the optimal cut-off was 80.3 cm3 for EFV, 2.4 cm3/m2 for EFVBMI and 41.7 cm3/(kg/m2) for EFVBSA. The optimal cut-off for EFVBSA was lower than the value 50 cm3/m2 reported by Ueno *et al*[16] (labeled VEAT in their series), despite a higher median value in our series: 53.7 cm3/m2 *vs* 47.1 cm3/m2. This difference is likely related to the definition of the end-point itself: significant CAD in the current study *vs* total occlusion of the coronary arteries in the series of Ueno *et al*[16]. More recently, Shmilovich *et al*[9] derived the threshold for the upper normal limit of indexed EF to BSA in a healthy population. The indexed EFV was also non-normally distributed, and the 75th-percentile was 47.1 cm3/m2, while in our series the 75th-percentile for the group 1 (composed of patients without CAD) 1 was 66.9 cm3/m2. Clearly, these values cannot be compared considering the major differences in the design of the two studies, the series of Shmilovich *et al*[9] including only asymptomatic patients with low risk and without clinical or biological risk factors for CAD.

Analysis of the correlation between the EFP and CT coronary angiography results revealed a trend of increase form group 1 to group 3. This result is similar to the conclusion of Taguchi *et al*[21] that pericardial fat is the strongest independent variable for the severity of CAD. Nevertheless, only groups 1 and 3 differed significantly. The overlap of values, for all EFP, between groups 2 and 3 may explain in great part the low specificity observed for the optimal cut-off. This point merits further analysis to achieve a higher predictive value of EF for significant CAD.

Relatively small number of studied patients with no available follow up data to observe the outcome or prognostic value of EFP considered a study limitation. Additionally our study may be affected by selection bias as we evaluate patients with clinical suspicion of CAD.

 In conclusion, the major outcome of the present study that the three methods for assessment of EF have the same equivalent predictive value for significant CAD and any one of them can be used as a sensitive predictor for significant CAD. Additionally, we provided a threshold for each one of the three EFP. For further validation of this threshold additional larger study is recommended.

**COMMENTS**

***Background***

Epicardial fat (EF) under normal physiological conditions, EF tissue displays biochemical, mechanical and thermogenic cardio protective properties. Under pathological circumstances, EF can be strongly related to the development of coronary artery disease (CAD). Several imaging modalities can be used to quantify EF volume (EFV) such as echocardiography, computed tomography, and magnetic resonance imaging

***Research frontiers***

ECG-gated cardiac computed tomography with its high spatial resolution and true volume coverage of the heart, allows accurate measurement of epicardial fat volumes. Besides EFV, some authors derived a second parameter, the body surface area indexed EFV (EFV/BSA); however, comparison between these two parameters has not been considered. Moreover, despite the predictive value of higher body mass index for cardiovascular event, the added value of body mass index (BMI)-adjusted EFV (EFV/BMI) also has not been previously assessed as well. The current study compares the predictive value of the three methods for EF assessment (EFV, EFV/BSA and EFV/BMI) for presence of significant CAD.

***Innovations and breakthroughs***

In the current study we compared the predictive value of three EFP for the presence of significant CAD. To our knowledge, no similar studies have been performed before and EFV/BMI has not previously assessed also, the predictive value of EF/VBSA for CAD has not been compared with EFV. The major outcome of the present study is that the three methods for assessing the EF have an equivalent predictive value for significant CAD. Furthermore we provided a threshold for each one of the three EF parameters.

***Applications***

Our study results suggested that; any one of the three methods for assessment of epicardial fat can be used to predict significant CAD since all have the same equivalent predictive value.

***Terminology***

EF is the visceral fat of the heart deposited under the visceral layer of the pericardium and has the same origin as abdominal visceral fat.

***Peer-review***

This is a good study in which the authors compare the predictive value of three methods used for quantification of epicardial fat [*i.e.,* EFV, EFV indexed with body surface area (EFV/BSA) and EFV indexed with body mass index (EFV/BMI)] for presence of significant CAD. The results are interesting and suggest that any one of the three methods for assessment of epicardial fat can be used to predict significant CAD since all have the same equivalent predictive value.

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**Figure 1 Measurement of Epicardial Fat Volume; the electronic line delineates the contour of epicardiumin in noncontrast computed tomography.**



**Figure 2 Measurement of epicardial fat Volume; the fat voxels were identified using threshold attenuation values (-30 to -190 HU) and the volume of epicardial fat is measures.**



**Figure 3 Receiver operating characteristic curves compare the three parameters for measuring the epicardial fat.** AUC was 0.62 for EFV, 0.6 for EFVBMI, and 0.61 for EFVBSA (non-significant pairwise comparison).



**Table 1 General characteristics of the patients among the three groups (total number of patients 170)*****n* (%)**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Group 1*****n* = 58** | **Group 2*****n* = 48** | **Group 3*****n* = 64** |  |
| Age | 48.5 (40.3-50.0) | 56 (48.5-64.5) | 55 (50- 62) | *P* = 0.004 |
| Male | 21 (36.2) | 32 (57.1) | 32 (50) | *P* = 0.008 |
| Hypertension | 24 (41.4) | 29 (60.4) | 37 (57.8) | *P* = 0.09 |
| Diabetes mellitus | 23 (39.7) | 34 (70.8) | 43 (67.2) | *P* = 0.001 |
| Smoking | 5 (8.6) | 4(8.3) | 14 (21.8) | *P* = 0.065 |
| Familial history | 7 (12.1) | 2 (4.2) | 6 (9.4) | *P* = 0.351 |
| BMI | 28.4 (25.9;-33.9) | 29.5 (25.9-33.1) | 31.6 (29.3 -33.1) | *P* = 0.007 |
| BSA | 1.80 (1.74-1.88) | 1.85 (1.78-1.94) | 1.88 (1.81- 1.95) | *P* = 0.093 |

BMI: Body mass index; BSA: Body surface area.

**Table 2 Comparison of three parameters for measuring the epicardial fat with computed tomography coronary angiography results**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Group 1** | **Group 2** | **Group 3** |  |
| EFV (cm3) | 81 (59.4-124) | 104 (83.5-126) | 113 (92-138) | *P* = 0.004 |
| EFVBMI (cm3/m2) | 2.7 (1.9-3.9) | 3.7 (2.5-4.3) | 3.8 (3.0-4.6) | *P* = 0.014 |
| EFVBSA[cm3/(kg/m2)] | 45.6 (35.3-66.9) | 53.9 (44.4-68.6) | 61.8 (48.1-75.4) | *P* = 0.011 |

EFV: Epicardial fat volume; EFVBMI: EFV indexed with body mass index; EFVBSA: EFV indexed with body surface area.