Original Article

Correlation of epicardial fat quantification with severity of coronary artery disease: A study in Indian population

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A B S T R A C T

Objective: We studied the correlation of quantified epicardial fat with severity of coronary artery disease in patients [suspected cases of coronary artery disease (CAD)] referred for computed tomography (CT) coronary angiography and established cutoffs for epicardial fat volume (EFV) for the presence of CAD and obstructive CAD.

Methods: A prospective cum retrospective cross-sectional observational study was carried out on 950 Indian subjects (suspected cases of CAD) who were referred for coronary CT in the year 2013–2016. EFV was quantified using semiautomatic technique on multidetector coronary CT angiography. The presence of atherosclerotic plaques and degree of stenosis was assessed on coronary CT angiography scans. The correlation between quantified EFV and degree of stenosis was assessed. Multivariate analysis was also performed.

Results: A higher quantity of epicardial fat is found in patients with increasing severity of coronary artery stenosis. The EFV cutoff for the presence of CAD and obstructive CAD are 49.75 and 67.69 mL with area under the curve, sensitivity, specificity, positive predictive value, negative predictive value, and diagnostic accuracy of 0.68, 81%, 45.9%, 58.24%, 72.2%, and 62.84% and 0.709, 64.9%, 66.4%, 35.84%, 86.55%, and 66%, respectively. EFV correlates with age, weight, and body mass index (BMI). Multivariate analysis revealed EFV to be an independent risk factor for the presence of CAD.

Conclusions: Higher quantities of EFV are found in patients with greater degree of coronary artery stenosis. EFV correlates with age, weight, and BMI. EFV is an independent risk factor for CAD.

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1. Introduction

Efforts have been made to identify new cardiovascular risk factors for detecting coronary artery disease (CAD). This has lead to the emergence of regional thoracic fat depots, epicardial fat in particular, as a strong CAD predictor. The fat depots around the heart can be classified into different compartments. Epicardial fat (EF) is the adipose tissue present between the myocardium and the pericardium, while paracardial fat refers to the mediastinal fat deposits located outside the parietal pericardium as depicted in Fig. 1. Pericardial fat refers to the sum of epicardial and paracardial fat deposits.6, 10

The physiological and beneficial roles of EF are immune barrier, myocardial and coronary artery protection, local fatty acid source for the myocardium, and predominate at normal quantities.2, 3 However, as the EF volume substantially increases, it becomes hypoxic and dysfunctional, characterized by increased lipolysis and consequent inflammation which eventually results into a shift in its metabolic profile and alters the homeostasis.4, 5 Therefore, it has been suggested to influence coronary atherosclerosis and progression of atherosclerotic plaques.6–10 EF can be easily and accurately quantified using multidetector computed tomography.
patients have a history of allergy to contrast media and tests were also seen in many cases. The symptoms included atypical chest pain, chest tightness, epigastric pain/burning, and jaw/shoulder pain. Dyspnea, worsening/reduced effort tolerance, new ECG abnormalities, and unequivocal stress tests were also seen in many cases.

Patients were asked to be fasting for 4 h before the contrast scan. The demographic data, cardiovascular risk factors, and the clinical signs and symptoms at the time of CT study were evaluated. The retrospective cases were obtained from the archived records. The weight and height parameters were available for 519 of 950 patients. For the lipid profile parameters, the cutoffs for serum low density lipoproteins (S.LDL, normal/high), serum high density lipoproteins (S.HDL, normal/low), and serum triglycerides (S.TG, normal/high) were taken as 100 mg/dL, 40 mg/dL, and 150 mg/dL, respectively.

Informed consent was obtained. CT angiography was not performed in patients with a history of allergy to contrast media and renal dysfunction (estimated glomerular filtration rate, eGFR<30 mL/min/1.73 m²). Moreover, patients with a history of open heart surgery, history of coronary artery stenting, postvalve replacement, pericardial effusion, and those with pacing leads were also excluded from our study. Necessary clearance was taken from the ethical committee of the hospital which follows the guidelines as mentioned under the Declaration of Helsinki.

A prospective cum retrospective cross-sectional observational study was carried out on 950 Indian subjects (suspected cases of CAD) who were referred for CT coronary angiography in the year 2013—2016. Patients of all ages who were referred for CT coronary angiography were screened for inclusion in the study. The patients presented with any constellation of clinical finding that the physician felt was consistent with CAD. The symptoms included atypical chest pain, chest tightness, epigastric pain/burning, and jaw/shoulder pain. Dyspnea, worsening/reduced effort tolerance, new ECG abnormalities, and unequivocal stress tests were also seen in many cases.

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All patients were in sinus rhythm at the time of the study. For a patient with heart rate (HR) >60 beats/min, steady HR of approximately 60 bpm was achieved using β-blockers agents and/or an anxiolytic. Calcium channel blocker was used if there was contra-indication to use β blockers. Patients were positioned feet first into the gantry. Sublingual sorbitrate (2.5 mg) was administered 2 min before scanning. Initial scout image was obtained. Prospective gated ECG-triggered noncontrast scan was acquired for coronary calcium scoring. Retrospective gated ECG-triggered contrast-enhanced cardiac CT angiography scan with intravenous administration of bolus of 80—110 mL of 350 mg/ml nonionic water-soluble contrast material [Omnipaque (iohexol) 350 mg/ml, GE Healthcare, Shanghai, China], injected using a dual head Medrad pressure injector at a flow rate of 5.5 ml/s through 18—20 G intravenous canula followed by saline flush of 20 ml, was acquired using low-dose 128-slice MDCT scanner (Ingenuity Philips, Philips Medical System, Netherlands). Acquisition was started from tracheal bifurcation (above the origin of the coronary arteries) and ended at the dome of the diaphragm. A bolus-triggering technique [trigger point with a threshold of 150 Hounsfield units (H.U.) placed in descending thoracic aorta] was used to synchronize the arrival of contrast in the coronary arteries with the initiation of scan. After manual adjustment of the field of view, data were reconstructed at various phases of cardiac cycle, keeping slice thickness: 0.8 mm and reconstruction increment: 0.4 mm in dedicated soft-tissue kernel settings and were analyzed followed by postprocessing. Curved multiplanar reformation, maximum intensity projection, volume-rendering technique images, 2D, and globe images were reconstructed, and all scans were analyzed on Philips workstation (Extended Brilliance Workspace; Philips). Correlation with conventional angiography was carried out wherever possible. EF was quantified using semiautomated technique (GE Advantage Window workstation) for measuring the amount of fat using contrast scans (end-systolic phase). A batch film was reconstructed keeping slice thickness: 3 mm and reconstruction increment: 1.5 mm. The chest area where EF is visualized was delimited by the upper slice limit: origin of the left main coronary artery and lower limit: cardiac apex (just below the posterior descending artery). The boundaries were manually traced. At the end, software recognized in the delimited area, the content with attenuation value between —30 and —250 H.U., characteristic of fatty tissue. This has been depicted in Fig. 2.

The degree of stenosis was classified as no stenosis (referred to as “CAD absent” in the study), nonobstructive (<50% stenosis), and obstructive (significant, >50% stenosis). For patients who had varying degrees of stenosis in different coronary artery segments, the plaque with the highest degree of stenosis was used for the classification of degree of stenosis. Patients who had evidence of CAD have been referred to as “CAD present” in the study.
2.2. Statistical methods

Statistical testing was performed using the Statistical Package for Social Sciences (SPSS) software, version 17.0. Continuous variables were presented as mean ± standard deviation or median (interquartile range). Categorical variables were expressed as frequencies and percentages. Kruskal–Wallis test/Mann–Whitney U test were used for comparing medians as the data were non-normally distributed. Spearman’s correlation coefficient was also estimated to assess the relation between different variables. Univariate and multivariate analysis was conducted. A receiver-operating characteristics (ROC) analysis was performed to determine optimal cutoff value of EFV for the presence of CAD and obstructive CAD. The area under the curve, sensitivity, and specificity were calculated to analyze the diagnostic accuracy. For all statistical tests, a p value less than 0.05 was taken to indicate a significant difference.

3. Results

A total of 950 patients were enrolled in this study. The mean age was 51.1 ± 11.23 years (age range 13–85 years). The number of males and females in the study were 623 (65.60%) and 327 (34.40%), respectively. The prevalence of various traditional cardiovascular risk factors such as smoking, hypertension, diabetes, and family history of CAD were 12.4%, 42.1%, 21.4%, and 23.2%, respectively. Among the patients having dyslipidemia, subjects having elevated S. LDL, low S.HDL, and elevated S.triglycerides were 22.2%, 6.7%, and 15.5%, respectively.

Majority of the patients had normal coronary angiograms (492, 51.8%) and were categorized into “CAD absent” group. The remainder (458, 48.2%) had evidence of CAD and were classified into the “CAD present” category. Patients in the “CAD present” group have been further classified into nonobstructive (<50% luminal narrowing/mild/nonsignificant stenosis, n = 244, 25.68%), and obstructive (>50% luminal narrowing/significant stenosis, n = 214, 22.53%) CAD group. The distribution of various patient characteristics in the “CAD absent” and “CAD present” groups have been projected in Table 1 along with their p values.

The prevalence of either of the traditional risk factors (smoking, hypertension, diabetes mellitus, family history of CAD, elevated serum cholesterol, elevated LDL, low serum HDL, elevated serum triglycerides) was significantly higher in the “CAD present” group as compared with the “CAD absent” group. No significant difference was seen in the distribution of weight and body mass index (BMI) between the two groups. The mean and median value of EFV was significantly higher in the “CAD present” group in comparison to the “CAD absent” group. Higher EFV was seen in patients with higher degrees of coronary artery stenosis (p <0.001). These results have been depicted in Table 2. Post hoc analysis revealed a significant difference in EFV in all 3 pairs of comparison (CAD absent vs. nonobstructive CAD, CAD absent vs. obstructive CAD, nonobstructive CAD vs. obstructive CAD).

On univariate analysis, it was observed that age, male gender, smoking, hypertension diabetes, family history of CAD, elevated serum LDL, low serum HDL, elevated serum triglycerides, coronary calcium score (CCS), and EFV were found to be significantly associated with the presence of CAD. On multivariate analysis, family history of CAD, CCS, and EFV were found to be independent predictors for the presence of CAD. The results have been depicted in Table 3.

ROC analysis was performed for determining optimal cutoff value of EFV for the presence of CAD and obstructive CAD. The cutoffs for EFV for the presence of (a) CAD and (b) significant CAD were estimated. The cutoffs along with area under the curve,
Table 1
Distribution of various patient characteristics in "CAD absent" and "CAD present" subjects.

| Patient characteristics | CAD absent (n = 492) | CAD present (n = 458) | p value |
|-------------------------|----------------------|----------------------|---------|
| Age (mean ± SD)         | 46.61 ± 10.446       | 55.91 ± 9.99         | <0.001  |
| Male gender             | 285 (57.9%)          | 338 (73.8%)          | <0.001  |
| Smoking                 | 37 (7.5%)            | 81 (17.7%)           | <0.001  |
| Hypertension            | 148 (30.1%)          | 252 (55.0%)          | <0.001  |
| Diabetes mellitus       | 65 (13.2%)           | 138 (30.1%)          | <0.001  |
| Family history CAD      | 92 (18.7%)           | 128 (27.9%)          | 0.001   |
| Dyslipidemia            |                      |                      |         |
| Cholesterol             | 92 (18.7%)           | 126 (27.5%)          | 0.007   |
| S.HDL                   | 92 (18.7%)           | 119 (26.0%)          | 0.001   |
| S.LDL                   | 18 (3.7%)            | 46 (10.0%)           | <0.001  |
| S.triglycerides         | 52 (10.6%)           | 95 (20.7%)           | <0.001  |
| Weight (n = 519\(^a\)) | 73.87 ± 10.84        | 75.12 ± 11.00        | 0.196   |
| BMI (n = 519\(^a\))    | 26.24 ± 3.674        | 26.21 ± 3.393        | 0.940   |
| EFV                     |                      |                      |         |
| Mean ± SD: 56.73 ± 27.63; median (IQR): 31.47; median (IQR): 84.55 | Mean ± SD: 75.308 ± 31.47; median (IQR): 69.152 (52.060–91.849) | <0.001  |

BMI, body mass index; CAD, coronary artery disease; EFV, epicardial fat volume; IQR, interquartile range; SD, standard deviation.

\(^a\) For parameters, weight and BMI, the sample size was 519 due to limited availability of data from the archived records in the retrospective cases.

Table 2
Regional thoracic fat volumes: Comparison between "CAD absent" vs. non-obstructive vs. obstructive CAD groups.

| "CAD absent" vs. nonobstructive CAD vs. obstructive CAD | EFV | p value |
|--------------------------------------------------------|-----|---------|
| Mean ± SD                                              | Median (IQR)   |
| CAD absent (492)                                       | 56.73 ± 27.63 | <0.001  |
| Obstructive CAD (214)                                  | 82.872 ± 32.32|         |
| Nonobstructive CAD (244)                               | 68.67 ± 29.18 |         |

CAD, coronary artery disease; EFV, epicardial fat volume; IQR, interquartile range; SD, standard deviation.

4. Discussion
Over the past few years, EFV has been implicated as a new risk factor for coronary atherosclerotic disease. Hence, its quantification is being considered to improve CAD risk prediction along with various traditional cardiovascular risk factors and coronary calcium scoring. The studies conducted in the USA by Rosito et al,\(^1\) Mahabadi et al,\(^2\) Ding et al,\(^3\) and Mahabadi et al\(^4\) and in Japan by Ito et al,\(^5\) comprised 1155, 1267, 998, 4093, and 1308 patients, respectively. To the best of our knowledge, this is the sixth largest study \((n = 950)\) on this topic across the globe and the first study conducted in the Indian subcontinent. We found that EFV was an

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Table 3
Univariate and multivariate analysis of risk factors in "CAD absent" vs. "CAD present" groups.

| Risk factors                     | Univariate analysis | Multivariate analysis |
|----------------------------------|---------------------|----------------------|
|                                  | Exp(B) [95% CI]     | p value              |
| Age                              | 2.365 [1.262–2.324] | <0.001               |
| Male gender                      | 2.046 [1.555–2.692] | <0.001               |
| Smoking                          | 2.642 [1.750–3.990] | <0.001               |
| Hypertension                     | 2.843 [2.178–3.712] | <0.001               |
| Diabetes mellitus                | 2.833 [2.040–3.935] | <0.001               |
| Family history CAD (FHCAD)       | 1.686 [1.243–2.288] | 0.001                |
| Dyslipidemia                     |                      |                      |
| Elevated S.LDL                   | 1.526 [1.121–2.077] | 0.007                |
| Low S.HDL                        | 2.940 [1.678–5.151] | <0.001               |
| Elevated S.triglycerides         | 2.214 [1.536–3.192] | <0.001               |
| Coronary calcium score (CCS total)| 1.552 [1.221–3.369] | <0.001               |
| EFV                              | 2.756 [1.221–3.789] | <0.001               |

CAD, coronary artery disease; CI, confidence interval; EFV, epicardial fat volume.

Table 4
Sensitivity, specificity, NPV, PPV, and diagnostic accuracy of thoracic fat volumes based on cutoffs in "CAD present vs. CAD absent" subjects and "obstructive vs. nonobstructive CAD".

| EFV cutoff values | Cutoff | AUC | Sensitivity | Specificity | PPV | NPV | Accuracy | p value |
|------------------|--------|-----|-------------|-------------|-----|-----|----------|---------|
| CAD present vs. CAD absent: EFV | 49.75  | 0.68| 81          | 45.9        | 58.24 | 72.2 | 62.84    | <0.001  |
| Obstructive vs. nonobstructive: EFV | 67.69 | 0.709| 64.9       | 66.4        | 35.84 | 86.55| 66       | <0.001  |

AUC, area under the curve; CAD, coronary artery disease; EFV, epicardial fat volume; PPV, positive predictive value; NPV, negative predictive value.
independent risk factor for CAD and showed higher values in patients with more severe CAD.

Quantification of EFVs was performed in all the patients (n = 950) using semi-automated technique. The range of fat attenuation threshold to characterize EF after pericardium tracing was from −30 to −250 H.U. as used by various studies in literature.16−19 Few studies have used −45 to −195 H.U. and −30 to −190 H.U. as the fat selection threshold.12,15 While some studies used contrast-enhanced coronary angiography scans for fat volume quantification, others used non-contrast scans (acquired for coronary calcium scoring) for carrying out the fat volume estimation.1,5,10,16,20,21 We estimated EFV on coronary angiography scans (end-systolic phase) and correlated these with the degree of coronary stenosis. Non-contrast scans can also be used where EFV can be estimated on scans acquired for calcium scoring.

The EFV showed correlation with age, BMI, and weight. Weaker correlations were observed with hypertension and diabetes, and no correlation was seen with other risk factors including smoking, family history of CAD, and elevated serum cholesterol. Similar results have been shown by Rosito et al11 and Alexopoulos et al.22 A similar association has also been observed by Yorgun et al23 who demonstrated that increased EF and pericoronary fat thickness is associated with the presence of metabolic syndrome. Patients having CAD were found to have a significantly higher EFV than those with no CAD. Moreover, the median fat volumes showed a significant ascending trend across the CAD severity groups, which is in accordance with previously published studies.12,19,22,24−27 Higher EFV has been observed in patients experiencing any major adverse cardiac event.28,29 Djafari et al had found significant relationship between EFV and the presence of CAD but failed to demonstrate a stepwise increase in EFV with increase in severity of atherosclerosis thereby suggesting EFV to be a qualitative and not a quantitative/semiquantitative CAD predictor.17 On multivariate analysis, we found EFV to be an independent risk factor for prediction of CAD after adjustments for various other traditional risk factors. Similar results have been shown by studies conducted in the past.11,12,14,28,29

In our study, the medians of various fat volumes across different CAD severity groups and their cutoffs in prediction of the presence of (i) CAD and (ii) significant CAD, are seen to be lower as compared with the rest of the studies in the literature. This might be due to varied methodology of EFV quantification and different patient cohorts. The findings of our study need to be confirmed in similar patient cohorts in India and in other cohorts across the globe in various ethnic groups with variable demographic and cardiovascular risk factor profiles.

On the contrary, few studies also exist in literature that have failed to demonstrate a significant association between regional fat volumes and atherosclerotic disease.30,31

5. Strengths and limitations of our study

The study was carried out in a large sample size (n = 950). Multiple variables were assessed, and univariate and multivariate analysis was conducted with other traditional cardiovascular risk factors which can act as confounders for CAD prediction. EFV showed correlation with age, weight, and BMI; however, no correlation was seen with smoking, elevated S. cholesterol, and family history of CAD. Moreover, EFV is an independent risk factor for CAD. We could also conclude that patients with raised EFV values had a higher degree of coronary stenosis.

However, there are several limitations that need to be acknowledged. Among the limitations, our study design was cross-sectional, and hence, our analysis was restricted to the evaluation of association between fat volume, CAD severity, and coronary plaque presence. The proatherogenic process, which relates the presence of higher quantities of regional fat and consequent predisposition to atherosclerosis, could not be investigated. Furthermore, no follow-up data could be studied. Hence, we cannot infer causality. The EFV values were correlated with CT coronary angiography for assessment of degree of stenosis and not catheter angiography which is taken as the gold standard. However, in our center, our CT coronary angiography studies have shown good correlation with catheter angiography findings. Moreover, we did not take abdominal fat and waist-hip ratio into consideration which are already established risk factors for CAD.

6. Conclusion

Various studies across the globe have analyzed the correlation of EF and CAD, and majority of them have suggested a significant association. Our study is in accordance with them, and we have suggested the cutoff values for patients at risk in the Indian population. EFV can be quantified by semi-automated technique using MDCT. The values are significantly higher across different CAD severity groups. EFV showed correlation with age, weight, and BMI. Multivariate analysis revealed EFV as an independent risk factor for CAD.

“Whether quantification of EFV has a prognostic value?” needs to be analyzed in prospective studies with long-term follow-up, in which we can contemplate the relationship between EFV with genesis of a new atherosclerotic plaque and eventual progression of an existing nonobstructing plaque to cause high-grade stenosis or complete occlusion. If similar results are also reflected in larger studies, across the globe in various ethnic groups, along with long-term outcomes and follow ups for CAD progression/major adverse cardiac events, the quantification and reporting of EFVs on CT coronary angiography will need consideration for adoption in our routine clinical practice as a test for CAD prediction, along with various traditional cardiovascular risk factor scores as well as coronary calcium scores.

6.1. What is already known?

Majority of the existing studies in literature have concluded EF to be an independent risk factor for CAD. Higher values of EF are found in patients with greater degree of stenosis.

6.2. What this study adds?

This is the first study conducted in the Indian subcontinent assessing the correlation of EFV with degree of CAD conducted on a large sample size. The cutoff values for EFV have been suggested to predict CAD and obstructive CAD in the Indian patients.

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Conflicts of interest

All authors have none to declare.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.ihj.2018.08.009.

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