Received:
11 May 2020

Revised:
14 July 2020

Accepted:
16 July 2020

<https://doi.org/10.1259/bjr.20200540>

Cite this article as:

Pandey NN, Sharma S, Jagia P, Kumar S. Epicardial fat attenuation, not volume, predicts obstructive coronary artery disease and high risk plaque features in patients with atypical chest pain. *Br J Radiol* 2020; **93**: 20200540.

FULL PAPER

Epicardial fat attenuation, not volume, predicts obstructive coronary artery disease and high risk plaque features in patients with atypical chest pain

NIRAJ NIRMAL PANDEY, MD, DNB, DM, SANJIV SHARMA, MD, PRIYA JAGIA, MD, DNB and SANJEEV KUMAR, MD

Department of Cardiovascular Radiology & Endovascular Interventions, All India Institute of Medical Sciences, New Delhi-110029, India

Address correspondence to: Dr Priya Jagia

E-mail: drpjagia@yahoo.com

Objective: This study sought to investigate the association between volume and attenuation of epicardial fat and presence of obstructive coronary artery disease (CAD) and high-risk plaque features (HRPF) on CT angiography (CTA) in patients with atypical chest pain and whether the association, if any, is independent of conventional cardiovascular risk factors and coronary artery calcium score (CACS).

Methods: Patients referred for coronary CTA with atypical chest pain and clinical suspicion of CAD were included in the study. Quantification of CACS, epicardial fat volume (EFV) and epicardial fat attenuation (EFat) was performed on non-contrast images. CTA was evaluated for presence of obstructive CAD and presence of HRPF.

Results: 255 patients (median age [interquartile range; IQR]: 51[41-60] years, 51.8% males) were included. On CTA, CAD, obstructive CAD ($\geq 50\%$ stenosis) and CTA-derived HRPFs was present in 133 (52.2%), 37 (14.5%) and 82 (32.2%) patients respectively. A significantly lower EFat was seen in patients with obstructive CAD than in those without (-86 HU [IQR: -88 to -82 HU] vs -84 [IQR: -87 HU to -82 HU]; $p = 0.0486$) and in patients with HRPF compared to those without (-86 HU [IQR: -88 to -83 HU] vs -83 HU [-86 HU to -81.750 HU]; $p < 0.0001$). EFat showed significant association with

obstructive CAD (unadjusted Odd's ratio (OR) [95% CI]: 0.90 [0.81-0.99]; $p = 0.0248$) and HRPF (unadjusted OR [95% CI]: 0.83 [0.76-0.90]; $p < 0.0001$) in univariate analysis, which remained significant in multivariate analysis. However, EFV did not show any significant association with neither obstructive CAD nor HRPF in multivariate analysis. Adding EFat to conventional coronary risk factors and CACS in the pre-test probability models increased the area-under curve (AUC) for prediction of both obstructive CAD (AUC [95% CI]: 0.76 [0.70-0.81] vs 0.71 [0.65-0.77]) and HRPF (AUC [95% CI]: 0.92 [0.88-0.95] vs 0.89 [0.85-0.93]), although not reaching statistical significance.

Conclusion: EFat, but not EFV, is an independent predictor of obstructive CAD and HRPF. Addition of EFat to traditional cardiovascular risk factors and CACS improves estimation for pretest probability of obstructive CAD and HRPF.

Advances in knowledge: EFat is an important attribute of epicardial fat as it reflects the "quality" of fat, taking into account the effects of brown-white fat transformation and fibrosis, as opposed to mere evaluation of "quantity" of fat by EFV. Our study shows that EFat is a better predictor of obstructive CAD and HRPF than EFV and can thus explain the inconsistent association of increased EFV alone with CAD.

INTRODUCTION

Epicardial fat is the fat contained within the pericardial sac encasing the epicardial coronary arteries without any intervening fascial barrier.^{1,2} It has been suggested that release of inflammatory cytokines from the epicardial fat exert a local paracrine pro-atherogenic effect on the adjacent coronary arteries by stimulating inflammation and recruitment of macrophages and B-lymphocytes.³⁻⁸ These processes have been linked to the development of coronary atherosclerosis as well as to the

occurrence of major adverse cardiovascular events.⁶⁻⁹

With epicardial fat being proposed as the link between dysregulated metabolism, coronary arterial inflammation and subsequent atherogenesis, there is considerable interest in the reported associations between epicardial fat volume (EFV) and presence of obstructive coronary artery disease (CAD) and presence of high-risk plaque features (HRPF).^{2,10-14} Few recent studies, however, did not find significant associations between EFV and CAD or revealed associations which did not remain significant

after adjustment for traditional cardiovascular risk factors, raising the question whether EFV indeed is an independent risk factor for CAD.^{15–18}

Epicardial fat attenuation (EFat), *i.e.* density of epicardial fat on CT, is another important attribute and may be more sensitive than EFV in detecting cardiovascular disease.¹⁹ Measuring EFat provides insight into the “quality” of fat, evaluating the effects of biological changes in epicardial fat like brown-white fat transformation and fibrosis, as opposed to mere evaluation of “quantity” of epicardial fat by EFV.^{20,21} EFat measurement may also help provide an answer as to why increased EFV alone shows inconsistent association with CAD. While lower attenuation of visceral and subcutaneous abdominal fat have been associated with increased coronary artery calcium scores (CACs) and adverse cardiovascular events in the Framingham Heart Study, the evidence linking EFat and the severity of CAD or presence of HRPf remains limited.^{21–23}

The present study aims to investigate the association between the volume and attenuation of epicardial fat and the severity of CAD and presence of HRPf on coronary CT angiography (CCTA) in patients with atypical chest pain and whether the association, if any, is independent of conventional cardiovascular risk factors and CACS.

METHODS AND MATERIALS

Study population

This prospective study was conducted with approval of our institutional review board, and all patients gave written informed consent. Between December, 2017 and August, 2018, adult patients referred for CCTA with complaints of atypical chest pain, clinical suspicion of CAD and no previous history of CAD (myocardial infarction, prior percutaneous coronary intervention or coronary artery bypass surgery) were included in the study. All patients underwent a prospective ECG-gated non-contrast scan (NCCT) for coronary artery calcium scoring followed by a retrospective ECG-gated CCTA for evaluating coronary artery stenosis. Patients with non-interpretable CTA were excluded from the study.

Co-variables

The conventional coronary risk factors were determined by preset criteria. Hypertension was defined as systolic blood pressure of ≥ 140 mmHg, diastolic blood pressure of ≥ 90 mmHg, or use of antihypertensive medication. Diabetes mellitus was defined as previously diagnosed case, patients on insulin or oral hypoglycemic therapy, fasting glucose of >126 mg dl⁻¹, or non-fasting glucose of >200 mg dl⁻¹. Family history of CAD was defined as history of myocardial infarction, percutaneous coronary intervention or coronary artery bypass surgery, or sudden cardiac death in a first-degree male relative <55 years old or female relative <65 years old.¹⁰ Hyperlipidemia was defined as total cholesterol of ≥ 220 mg dl⁻¹, low-density lipoprotein cholesterol of ≥ 140 mg dl⁻¹, fasting triglycerides of ≥ 150 mg dl⁻¹, or receiving treatment with lipid-lowering drugs.²⁴ Smoking was defined as current smoking or smoking in past 6 months.²⁴

CT acquisition protocol

All examinations were performed on Somatom Force (Siemens Healthcare, Forchheim, Germany) CT scanner. A prospective ECG-gated sequential NCCT acquisition was obtained at 70% of R–R interval using the following parameters: tube voltage -120 kV; automated tube current modulation (CARE Dose4D, Siemens Healthcare, Forchheim, Germany) with reference tube current - 80 mAs. Images were reconstructed with section thickness and increments of 3 mm, using Qr36 kernel, with a model-based iterative reconstruction strength level 3 (ADMIRE; Siemens Healthcare, Forchheim, Germany).

A retrospective ECG-gated CCTA examination was performed in all subjects. Non-ionic iodinated contrast (Omnipaque 350, GE Healthcare, Princeton, NJ; 1.0 mL/kg body weight) was injected via peripheral intravenous line using a dual head power injector at flow rate of 5 ml s⁻¹ followed by 40 ml saline chaser. CT acquisition was triggered when contrast attenuation in the ascending aorta reached 100 Hounsfield units (HU) on the monitoring sequence. Automated tube voltage selection and automated tube current modulation based on body habitus (CARE kV and CARE Dose4D, Siemens Healthcare, Forchheim, Germany) were employed. Slices were reconstructed of 0.6 mm section thickness and increment of 0.4 mm, using a medium sharp kernel (Bv40), with a model-based iterative reconstruction strength level 3 (ADMIRE; Siemens Healthcare, Forchheim, Germany). The CT studies were evaluated by observers having more than 10 years' experience in the field of cardiac imaging.

Coronary artery calcium scoring

Quantification of coronary artery calcium was performed on NCCT images using Agatston method utilizing the software developed for semi-automatic assessment of coronary calcium (Application: Calcium scoring; syngo.via, Siemens Healthcare, Forchheim, Germany). The software predefines areas with attenuation ≥ 130 HU and allows the user to select the calcification supposed to be related to coronary arteries.

Assessment of EFV and EFat

Epicardial fat was defined as fat contained within the pericardial sac. EFV and EFat were measured offline using NCCT images on an external workstation (Syngo.via; Siemens Healthcare, Forchheim, Germany) utilizing a semi-automated technique. Region of interest (ROI) were drawn for all patients by manual tracing of the pericardium in axial planes from the take-off of right pulmonary artery to apex of heart at 1 cm intervals. As suggested in previous literature, attenuation thresholds of -190 and -30 HU were applied within the ROI to identify voxels containing fat.^{25–27} EFV and EFat were recorded in cubic centimeters (cc) and the mean HU respectively (Figure 1). To study reproducibility and interobserver variability, EFV and EFat of 30 randomly chosen subjects were independently measured by two independent observers. Both observers had more than 10 years' experience in the field of cardiac imaging.

Analysis of CCTA

Reconstructed CCTA data sets were transferred to an offline workstation (Syngo.via; Siemens Healthcare, Forchheim, Germany),

Figure 1. Measurement of epicardial fat volume and epicardial fat attenuation. (A, B) The pericardium (arrows) is identified and multiple contour points are placed along the pericardium on multiple axial sections from the upper limit to the lower limit. (C, D) The software identifies all pixels within the volume-of-interest between -190 HU to -30 HU as epicardial fat (highlighted in green color in D) and automatically calculates the volume and mean attenuation, in cubic centimeters and HU respectively. HU, Hounsfield unit.

and coronary artery segments were evaluated for the presence of plaque, type of plaque (calcified, non-calcified and mixed), presence of obstructive CAD (at least one lesion causing luminal stenosis of $\geq 50\%$) and presence of HRPF. HRPF were defined as positive remodeling (maximal outer arterial wall diameter along the plaque exceeding the average diameter of the proximal and distal normal reference vessel by $\geq 10\%$), low-attenuation-plaque (visually distinct intra plaque hypoattenuation containing HU ≤ 30) and spotty calcification (calcified plaque < 3 mm, length of calcium burden < 1.5 times the vessel diameter and width $< 2/3$ rd of vessel diameter).

Statistical analysis

All statistical analysis used MedCalc Statistical Software v. 18.2.1 (MedCalc Software bvba, Ostend, Belgium; <http://www.medcalc.org>; 2018). For all tests, p -value of < 0.05 was considered to indicate statistical significance. Continuous variables were expressed as median and interquartile range (IQR) and compared between groups using Mann–Whitney U test. Categorical variables were expressed as frequencies with percentages and compared using chi-square or Fisher's exact test, as appropriate. Interobserver

variability for EFV and EFat was assessed using intraclass correlation coefficient (ICC; model: two-way random effects, definition: absolute agreement, type: single rater/measurement). Based on 95% confidence interval (CI) of ICC estimate, the reliability was graded as follows: < 0.50 : poor, 0.50 – 0.75 : moderate, 0.75 – 0.90 : good and > 0.90 : excellent. When the distribution of variables was not normal, the degree of association between the variables was calculated using rank correlation (Spearman's correlation coefficient, ρ).

To provide a potentially clinically useful threshold for EFV and EFat, optimal cut-off values regarding obstructive CAD and HRPF were calculated using receiver operating characteristic (ROC) curve analysis. To determine the association between presence of obstructive CAD & HRPF and EFV & EFat, univariate (unadjusted) and multivariate (adjusted) logistic regression analyses was performed. The models included presence of obstructive CAD and presence of HRPF as dependent variables respectively, while absolute EFV, body surface area (BSA)-indexed EFV, EFat, age, sex, body mass index (BMI), hypertension, hyperlipidemia,

Table 1. Baseline characteristics of the patient population ($n = 255$)

Age (years) ^a	51(46-60)
Males*	132 (51.8%)
Body mass index (kg/m ²) ^a	26.45 (23.44–29.64)
Family history of coronary artery disease*	64 (25.1%)
Diabetes*	55 (21.6%)
Hypertension*	195 (76.5%)
Hyperlipidemia*	110 (43.1%)
Smoker*	17 (6.7%)
CACS (AU) = 0*	166 (65.1%)
CACS (AU) >0*	89 (34.9%)
CACS >0 and ≤10*	28 (11.0%)
CACS >10 and ≤100*	44 (17.3%)
CACS >100*	17 (6.7%)
Epicardial fat volume (cc) ^a	104.88 (79.52–131.91)
Indexed epicardial fat volume (cc/m ²) ^a	60.093 (48.04–75.01)
Epicardial fat attenuation (HU) ^a	–84 (–87 to –82)
Presence of at least one coronary artery plaque*	133 (52.2%)
Presence of at least one coronary artery plaque causing ≥50% stenosis*	37 (14.5%)
Presence of at least one coronary artery plaque causing ≥70% stenosis*	24 (9.4%)
Presence of at least 1 CT-derived high-risk plaque features*	82 (32.2%)
Positive remodeling*	34 (13.3%)
Low-attenuation plaque*	20 (7.8%)
Spotty calcification*	47 (18.4%)

CACS: coronary artery calcium score; HU: Hounsfield's unit; AU: Agatston unit

^avalues in median (interquartile range), *values in $n(\%)$.

diabetes mellitus, family history of CAD, smoking and CACS were included as independent variables.

RESULTS

A total of 255 Indian patients (median age [IQR]: 51[41–60] years, 52% males) were included in the study. The baseline characteristics of the study population are presented in Table 1. On CCTA, CAD was present in 133 (52%) patients with obstructive CAD seen in 37 (15%) patients. Coronary artery calcium was seen in 89 (35%) patients. At least one CT-derived HRPf was observed in 82 (32%) patients.

Excellent inter-rater agreement between the two readers was seen for EFV (ICC = 0.99; 95% CI: 0.98–0.99) and good inter-rater agreement was seen for EFat (ICC = 0.92; 95% CI: 0.83–0.96). The randomly chosen subset was representative of the study population with no significant difference between the EFV (median [IQR]: 111.36 [81.53–131.89] vs 104.88 [79.52–131.91];

$p = 0.5272$) and EFat values (median [IQR]: –85 [–87 to –83] vs. –84 [–87 to –82]; $p = 0.1673$) of the random subset and the overall study population.

Association between EFV and EFat

There was no significant correlation between EFV and EFat ($\rho = -0.12$; $p = 0.0576$) in the overall study population.

Association between EFV and conventional CAD risk factors

The median EFV was 104.88cc (IQR:79.515–131.905) and showed significant correlation with increasing age ($\rho = 0.31$; $p < 0.0001$) and BMI ($\rho = 0.39$; $p < 0.0001$), although correlation co-efficient was low. Association with other conventional CAD risk factors is depicted in Supplementary Table 1.

Association between EFat and conventional CAD risk factors

The median EFat was –84 HU (IQR: –87 to –82) and did not show significant correlation with increasing age ($\rho = -0.09$; $p = 0.1586$) or BMI ($\rho = 0.06$; $p = 0.3329$). Association with other conventional CAD risk factors is depicted in Supplementary Table 1.

Association of EFV and EFat with presence of obstructive CAD

EFV was not significantly different between patients with obstructive CAD and those without an obstructive CAD (116.98 cc [IQR:84.08–139.365] vs 102.65 cc [IQR:79.33–131.02]; $p = 0.2960$). Similarly, the EFV, indexed to BSA, was also not significantly different between the two groups (65.04 cc [IQR:47.916–75.761] vs 59.738 cc [IQR:48.046–74.127]; $p = 0.3148$). However, patients with obstructive CAD had a significantly lower median EFat than those without an obstructive CAD (–86 HU [IQR: –88 to –82] vs –84 HU [IQR: –87 to –82]; $p = 0.0486$). (Figure 2, Table 2).

On univariate analysis, both EFV (unadjusted Odds ratio, OR [95% CI]=1.01 [1.00–1.01]; $p = 0.2361$) and indexed EFV (unadjusted OR [95% CI]=1.01 [0.99–1.03]; $p = 0.2385$) were not significantly associated with presence of obstructive CAD. EFat showed significant association with obstructive CAD in univariate analysis (unadjusted OR [95% CI]=0.90 [0.81–0.99]; $p = 0.0248$). On multivariate logistic regression analysis for predictors of obstructive CAD, EFat (adjusted OR [95% CI]=0.89 [0.80–0.99]; $p = 0.0330$), CACS >10–100 (adjusted OR [95% CI]=4.22 [1.63–10.95]; $p = 0.0031$) and CACS >100 (adjusted OR [95% CI]=7.64 [1.94–30.09]; $p = 0.0037$) were significant independent predictors. (Table 3)

The optimal threshold of EFat for prediction of obstructive CAD was ≤86HU which was significantly associated with obstructive CAD (unadjusted OR [95% CI]=2.05 [1.02–4.15]; $p = 0.0448$). On backward stepwise logistic regression analysis, the association remained significant (adjusted OR [95% CI]=2.13 [1.03–4.40]; $p = 0.0404$) after adjustment for presence of hyperlipidemia (adjusted OR [95% CI]=2.08 [1.01–4.29]; $p = 0.0469$) and diabetes mellitus (adjusted OR [95% CI]=2.47 [1.13–5.38];

Figure 2. 47 year old female (categorized as being at intermediate risk according to the Framingham risk score) presenting with atypical chest pain. Measurement of epicardial fat by semi-automated method with the fat depicted in green in the axial image (A) and in pink in the volume rendered images (B, C) reveals epicardial fat volume to be 58.14 cc with the epicardial fat attenuation to be -88HU . (D) Curved multiplanar reformatted image centered on the left anterior descending (LAD) artery shows a circumferential low attenuation non-calcified plaque (white arrow) in the proximal-to-mid LAD artery causing approximately 80% stenosis with positive remodeling of the involved segment of LAD artery.

$p = 0.0227$). Age, sex, BMI, presence of hypertension, family history of CAD and smoking status were excluded from the model as they did not meet the criteria of $p < 0.1$.

We defined and tested three pre-test probability (PTP) models: Model A: conventional cardiovascular risk factors (age + sex + BMI + hypertension + hyperlipidemia + diabetes mellitus + family history of CAD + smoker); Model B: Model A + CACS; Model C: Model B + EFat (as a binary marker). On comparison of three PTP models for prediction of obstructive CAD, model C had the largest area under curve (AUC [95% CI]=0.76 [0.70–0.81]) when compared to either model A (AUC [95% CI]=0.66 [0.60–0.72]) or model B (AUC [95% CI]=0.71 [0.65–0.77]), although the difference was not statistically significant. (Supplementary Table 2).

Association of EFV and EFat with presence of HRPF

Patients with any HRPF had a statistically significant higher median EFV than those without (119.94 cc [IQR:90.71–151.560] vs 95.90 cc [IQR:76.818–121.382]; $p < 0.0001$). Similarly, the median indexed EFV was also significantly higher in patients with HRPF (67.859 cc [IQR: 53.42–81.713] vs 56.546 cc [IQR:46.265–71.438]; $p = 0.0004$). Patients with HRPF had a significantly lower median EFat than those without any HRPF (-86 HU [IQR: -88 to -83] vs -83 HU [-86 to -81.750]; $p < 0.0001$) (Figure 2, Table 2).

A lower median EFat showed significant association with the presence of positive remodeling (unadjusted OR [95% CI]=0.84 [0.76–0.94]; $p = 0.0013$), low-attenuation-plaque (unadjusted OR [95% CI]=0.88 [0.78–1.00]; $p = 0.0455$) as well as spotty calcification (unadjusted OR [95% CI]=0.90 [0.82–0.98]; p

$= 0.0177$). However, a higher median EFV showed a significant association only with spotty calcification (unadjusted OR [95% CI]=1.02 [1.01–1.02]; $p = 0.0002$) while the association with positive remodeling (unadjusted OR [95% CI]=1.00 [0.99–1.01]; $p = 0.6227$) and low-attenuation-plaque (unadjusted OR [95% CI]=1.01 [0.99–1.02]; $p = 0.3482$) was not statistically significant.

In univariate analysis, all three EF-related variables including EFV (unadjusted OR [95% CI]=1.01 [1.01–1.02]; $p = 0.0001$), indexed EFV (unadjusted OR [95% CI]=1.02 [1.01–1.04]; $p = 0.0008$) and EFat (unadjusted OR [95% CI]=0.83 [0.76–0.90]; $p < 0.0001$) were significantly associated with presence of HRPF. However, in multivariate logistic regression analysis, of the three, only EFat (adjusted OR [95% CI]=0.72 [0.61–0.85]; $p = 0.0001$) remained a significant independent predictor of HRPF. (Table 4)

Based on ROC curve analysis, the optimal threshold of EFat for prediction of HRPF was $\leq 83\text{ HU}$ which was significantly associated with presence of HRPF (unadjusted OR [95% CI]=3.51 [1.77–6.97]; $p = 0.0003$). On backward stepwise logistic regression analysis, the association remained significant after adjustment for age (adjusted OR [95% CI]=1.06 [1.03–1.10]; $p = 0.0003$), male gender (adjusted OR [95% CI]=2.50 [1.32–4.73]; $p = 0.0048$), BMI (adjusted OR [95% CI]=1.06 [1.00–1.13]; $p = 0.0624$) and presence of diabetes mellitus (adjusted OR [95% CI]=3.86 [1.91–7.77]; $p = 0.0002$). Presence of hypertension, hyperlipidemia, family history of CAD and smoking status were excluded from the model as they did not meet the criteria of $p < 0.1$.

On comparing the three previously described PTP models for prediction of HRPF, once again, model C had the largest area

Table 2. Comparison of risk factors in patients with and without coronary artery disease, in patients with and without obstructive coronary artery disease (presence of at least one plaque causing $\geq 50\%$ stenosis) and in patients with and without CT-derived high risk plaque features

Risk factors	Patients with CAD (n = 133)	Patients without CAD (n = 122)	p-value	Patients with obstructive CAD (n = 37)	Patients without obstructive CAD (n = 218)	p-value	Patients with HRPFs (n = 82)	Patients without HRPFs (n = 173)	p-value
Age (in years) ^a	55 (48.75–63.25)	48 (42–54)	<0.0001	51 (47–64)	51 (45–60)	0.1495	56 (49–63)	50 (44–57.25)	0.0001
Males*	80 (60.2%)	52 (42.6%)	0.0050	20 (54.1%)	112 (51.4%)	0.7617	52 (63.4%)	80 (46.2%)	0.0104
BMI (in kg/m ²) ^a	27.22 (24.48–29.76)	26.14 (22.41–29.24)	0.0529	26.37 (24.02–28.91)	26.52 (23.42–29.90)	0.8348	27.14 (24.89–29.68)	26.35 (22.77–29.64)	0.1789
Family history of CAD*	34 (25.6%)	30 (24.6%)	0.8544	11 (29.7%)	53 (24.3%)	0.4844	20 (24.4%)	44 (25.4%)	0.8636
Diabetes*	41 (30.8%)	14 (11.5%)	0.0002	13 (35.1%)	42 (19.3%)	0.0311	30 (36.6%)	25 (14.5%)	0.0001
Hypertension*	106 (79.7%)	89 (73%)	0.2084	32 (86.5%)	163 (74.8%)	0.1214	64 (78.0%)	131 (75.7%)	0.6866
Hyperlipidemia*	63 (47.4%)	47 (38.5%)	0.1525	22 (59.5%)	88 (40.4%)	0.0304	36 (43.9%)	74 (42.8%)	0.8687
Smoker*	9 (6.8%)	8 (6.6%)	0.9492	2 (5.4%)	15 (6.9%)	0.7360	5 (6.1%)	12 (6.9%)	0.8110
EFV (in cc) ^a	113.82 (84.73–141.96)	96.01 (78.25–120.23)	0.0021	116.98 (84.08–139.37)	102.65 (79.33–131.02)	0.2960	119.94 (90.71–151.56)	95.90 (76.82–121.38)	<0.0001
Indexed EFV (in cc/m ²)	63.18 (49.80–78.45)	56.50 (46.50 to 71.27)	0.0130	65.04 (47.92–75.76)	59.74 (48.05–74.13)	0.3148	67.86 (53.42–81.71)	56.55 (46.27–71.44)	0.0004
EFat (in HU) ^a	–85 (–87 to –82.75)	–84 (–86 to –82)	0.0108	–86 (–88 to –82)	–84 (–87 to –82)	0.0486	–86 (–88 to –83)	–83 (–86 to –81.750)	<0.0001
Presence of CAC*	-	-	-	23 (62.2%)	66 (30.3%)	0.0002	66 (80.5%)	23 (13.3%)	<0.0001
CACS >0 and ≤ 10 *	-	-	-	3 (8.1%)	25 (11.5%)	0.5420	26 (31.7%)	2 (1.2%)	<0.0001
CACS >10 and ≤ 100 *	-	-	-	14 (37.8%)	30 (13.8%)	0.0004	33 (40.2%)	11 (6.4%)	<0.0001
CACS >100*	-	-	-	6 (16.2%)	11 (5.0%)	0.0115	7 (8.5%)	10 (5.8%)	0.4204
Obstructive CAD*	-	-	-	-	-	-	29 (35.4%)	8 (4.6%)	<0.0001

CAD: coronary artery disease; HU: Hounsfield's unit; BMI: body mass index; EFV: epicardial fat volume; EFat: epicardial fat attenuation; HRPF: high risk plaque features; CAC: coronary artery calcification; CACS: coronary artery calcium score
^avalues in median (interquartile range). *values in n (%).

Table 3. Univariate and multivariate logistic regression analysis for predictors of obstructive coronary artery disease

Independent variables	Univariate analysis		Multivariate analysis model (including absolute EFV)		Multivariate analysis model (including indexed EFV)	
	Unadjusted OR (95% CI)	<i>p</i> -value	Adjusted OR (95% CI)	<i>p</i> -value	Adjusted OR (95% CI)	<i>p</i> -value
EFV	1.01 (1.00–1.02)	0.2361	1.00 (0.99–1.01)	0.6062	--	--
Indexed EFV	1.01 (0.99–1.03)	0.2385	--	--	1.00 (0.98–1.02)	0.7044
EFat	0.90 (0.81–0.99)	0.0248	0.89 (0.80–0.99)	0.0330	0.89 (0.80–0.99)	0.0329
Age	1.03 (1.00–1.07)	0.0685	0.99 (0.95–1.04)	0.7673	0.99 (0.95–1.04)	0.7907
Male gender	1.11 (0.55–2.24)	0.7632	0.77 (0.33–1.75)	0.5281	0.80 (0.35–1.81)	0.5932
BMI	0.99 (0.92–1.06)	0.8073	0.95 (0.86–1.04)	0.2599	0.95 (0.87–1.04)	0.2833
Hypertension	2.16 (0.80–5.82)	0.1278	2.01 (0.69–5.90)	0.2021	2.01 (0.69–5.89)	0.2037
Hyperlipidemia	2.17 (1.07–4.41)	0.0328	1.86 (0.86–4.03)	0.1143	1.86 (0.86–4.03)	0.1135
Diabetes mellitus	2.27 (1.07–4.83)	0.0332	1.74 (0.76–3.99)	0.1934	1.74 (0.76–4.00)	0.1931
Family history of CAD	1.32 (0.61–2.84)	0.4832	1.23 (0.54–2.80)	0.6215	1.23 (0.54–2.80)	0.6205
Smoker	0.77 (0.17–3.53)	0.7400	0.91 (0.17–4.72)	0.9087	0.90 (0.17–4.68)	0.9010
Coronary artery calcium score (CACS)						
>0 to ≤10	1.30 (0.35–4.86)	0.6937	1.15 (0.28–4.80)	0.8442	1.17 (0.28–4.85)	0.8287
>10 to ≤100	5.07 (2.19–11.71)	0.0001	4.22 (1.63–10.95)	0.0031	4.23 (1.63–10.98)	0.0030
>100	5.92 (1.90–18.43)	0.0021	7.64 (1.94–30.09)	0.0037	7.60 (1.91–30.25)	0.0040

EFV: epicardial fat volume; EFat: epicardial fat attenuation; OR: Odds ratio; CI: confidence interval; BMI: body mass index; CAD: coronary artery disease

Table 4. Univariate and multivariate logistic regression analysis for predictors of high risk plaque features

Independent variables	Univariate analysis		Multivariate analysis model (including absolute EFV)		Multivariate analysis model (including indexed EFV)	
	Unadjusted OR (95% CI)	<i>p</i> -value	Adjusted OR (95% CI)	<i>p</i> -value	Adjusted OR (95% CI)	<i>p</i> -value
EFV	1.01 (1.01–1.02)	0.0001	1.01 (1.00–1.03)	0.1832	--	--
Indexed EFV	1.02 (1.01–1.04)	0.0008	--	--	1.01 (0.99–1.04)	0.3286
EFat	0.83 (0.76–0.90)	<0.0001	0.72 (0.61–0.85)	0.0001	0.72 (0.61–0.85)	0.0001
Age	1.06 (1.03–1.10)	<0.0001	0.99 (0.93–1.05)	0.6713	0.99 (0.93–1.05)	0.7010
Male gender	2.02 (1.17–3.46)	0.0109	2.54 (0.81–7.97)	0.1105	2.98 (0.99–8.96)	0.0524
BMI	1.04 (0.98–1.09)	0.1844	1.08 (0.96–1.21)	0.2005	1.10 (0.99–1.23)	0.0845
Hypertension	1.14 (0.61–2.14)	0.6826	0.51 (0.16–1.64)	0.2594	0.51 (0.16–1.65)	0.2639
Hyperlipidemia	1.05 (0.62–1.78)	0.8651	0.30 (0.10–0.91)	0.0339	0.31 (0.10–0.93)	0.0367
Diabetes mellitus	3.42 (1.84–6.33)	0.0001	4.41 (1.50–13.01)	0.0072	4.46 (1.51–13.19)	0.0068
Family history of CAD	0.95 (0.51–1.74)	0.8576	0.58 (0.18–1.81)	0.3452	0.60 (0.19–1.86)	0.3780
Smoker	0.87 (0.30–2.56)	0.8021	1.25 (0.21–7.56)	0.8070	1.21 (0.20–7.25)	0.8347
CACS						
CACS >0 to ≤10	121.88 (26.45–561.62)	<0.0001	890.45 (90.03–8807.44)	<0.0001	841.26 (87.55–8083.26)	<0.0001
CACS >10 to ≤100	28.13 (11.96–66.15)	<0.0001	45.12 (12.51–162.75)	<0.0001	44.15 (12.38–157.40)	<0.0001
CACS >100	6.56 (2.20–19.61)	0.0008	5.67 (1.05–30.66)	0.0437	5.68 (1.04–31.09)	0.0451
Obstructive CAD	11.29 (4.86–26.19)	<0.0001	37.21 (9.37–147.78)	<0.0001	36.16 (9.18–142.40)	<0.0001

BMI: body mass index; CACS, coronary artery calcium score; CAD: coronary artery disease; CI: confidence interval; EFV: epicardial fat volume; EFat: epicardial fat attenuation; OR: Odds ratio.

under curve (AUC [95% CI]=0.92 [0.88–0.95]) when compared to either model A (AUC [95% CI]=0.74 [0.68–0.79]) or model B (AUC [95% CI]=0.89 [0.85–0.93]); however, the difference was not statistically significant. (Supplementary Table 3)

DISCUSSION

The current study showed that in patients of atypical chest pain without known CAD undergoing CCTA, EFV was not a significant predictor for obstructive CAD in either univariate or multivariate logistic regression analysis. EFat, on the other hand, remained a significant predictor of obstructive CAD, even after adjustment for the conventional cardiovascular risk factors and CACS. While both EFV and EFat were significant predictors of HRPF in univariate analysis, in multivariate analysis, only EFat remained a significant predictor after adjusting for potential confounders like cardiovascular risk factors, CACS, and presence of obstructive CAD. Addition of EFat to conventional risk factors and CACS offered a more accurate and effective estimation of pretest probability of obstructive CAD and HRPF. These factors suggest that EFat could be a vital characteristic that could outline the role of epicardial fat in the development and progression of CAD.

Adipocyte hypertrophy leading to a reduced capillary density can induce hypoxia resulting in necrosis in epicardial fat and might elicit an inflammation process to induce coronary atherosclerosis by virtue of its direct contact with the epicardial coronary arteries.²⁸ The other mechanism underlying the association of epicardial fat with CAD includes a disordered secretory profile with accumulation of inflammatory mediators secreted by the infiltrating macrophages, which may further stimulate and augment interstitial fibrosis in epicardial fat.^{21,29–31} These inflammatory mediators in the perivascular fat may lead to amplification of vascular inflammation and plaque instability via apoptosis and neovascularization.³⁰

While fat expansion caused by adipocyte hypertrophy and hyperplasia decreases EFat, it is proposed that presence of interstitial fibrosis in the epicardial fat would result in increased EFat secondary to increased accrual and deposition of extracellular matrix.^{21,32–34} In our study, a more negative EFat was associated with obstructive CAD and HRPF. This is in sync with the observations of other studies which have shown that lower attenuation values of epicardial fat are linked with coronary calcification, serum levels of plaque inflammatory markers and major adverse cardiac events as well as studies investigating association of visceral and subcutaneous fat with CAD.^{19,22,28,35} However, few studies have reported contrary findings where higher EFat is associated with impaired CAD profile and adverse cardiac events.^{21,36,37} In the study by Liu Z et al including 614 patients, they observed that a higher epicardial fat attenuation was associated with a higher risk of CAD. The mean epicardial fat volume in their study population was 84 ± 37 cc compared to 109 ± 39 cc (median [IQR]: 104.88 cc [79.52–131.91]) in our study.²¹ The contradicting findings can possibly be explained by the hypothesis that adipocyte expansion and fibrosis occur concurrently in epicardial fat and that the effect of fibrosis on EFat will be largely determined by the base EFV. In the presence of smaller

EFVs, even small amounts of fibrosis may result in significant increase in EFat as the effect of fibrosis on EFat (*i.e.* increase in attenuation) would predominate over the effect caused by adipocyte hypertrophy and hyperplasia (*i.e.* decrease in attenuation).²¹ Conversely, in larger EFVs, the effect of adipocyte hypertrophy and hyperplasia on EFat would predominate over fibrosis resulting in lower EFat values. Variation in the degrees of inflammation and fibrosis experienced by the different study populations could also possibly explain the divergent findings.²¹

Contrary to previous studies conducted by Lu et al, Rajani et al, Sarin et al, Iwasaki et al and Ueno et al, we did not find a significant association between EFV and the presence of obstructive CAD or HRPF.^{2,10–13} This lack of association of EFV with the studied outcomes could conceivably be expounded by the characteristics of our relatively homogenous study cohort which comprised of patients with atypical chest pain referred for CCTA to rule out CAD, thus placing our patients in a low-to-intermediate risk group in contrast to other studies with study subjects having a more heterogeneous risk profile and quality of chest pain. Another explanation could be the fact that our entire study cohort was drawn from the Indian population. Fat distribution in general, and epicardial fat in particular, varies across different ethnic groups and may have a bearing on the relationship of EFV with markers of CAD severity.¹⁵ Nevertheless, we should stress upon the fact that, in the present study, we did not investigate the relationship with adverse cardiovascular events, but rather with the severity of CAD and presence of HRPF. It is plausible that rather than directly influencing atherosclerotic burden, EFV may play a role in influencing vascular functions in response to plaque alterations.^{15,34} Various previous studies have linked EFV with increased risk of adverse clinical events; since the clinical outcome, rather than mere presence of obstructive disease or HRPF, is more important, the present results should not abrogate the conceivable impact of EFV for clinical decision-making and management.^{15,31,38–40}

Our study has several limitations. Firstly, as a cross-sectional observational study, we could only infer associations and not establish a cause-effect relationship between epicardial fat attributes and outcome measures. Secondly, this was a single-centre study conducted in Indian population, and results may differ for other ethnic groups. Thirdly, we only assessed correlations between epicardial fat parameters (assessed by CT) and other parameters like presence of obstructive CAD and HRPF (also assessed by CT); however, no follow-up data for adverse cardiac events were available in the current study and follow-up studies of the cohort would be required to further evaluate the prognostic potential of EFat. Fourthly, the number of patients with obstructive CAD is relatively small. Lastly, while we showed that EFat was related to obstructive CAD and HRPF independently of other potential confounders, there could be other relevant factors that were not accounted for in our study.

To conclude, EFat, but not EFV, is an independent predictor for the presence of obstructive CAD and HRPF in patients presenting with atypical chest pain, without known CAD. Addition of EFat to traditional cardiovascular risk factors and CACS offers a

more accurate and effective estimation for pretest probability of obstructive CAD and HRPf, which may help to improve the initial management of atypical chest pain with suspected CAD. Since EFat is derived from the same NCCT used for quantifying CACS, it may also allow for better definition of cardiovascular risk from unenhanced scans. As EFat reflects the changes in the

composition of epicardial fat, it may serve as a beneficial complementary indicator in revealing the role of epicardial fat in CAD.

FUNDING

Authors received no financial support for the research, authorship, and/or publication of this article.

REFERENCES

1. Fitzgibbons TP, Czech MP. Epicardial and perivascular adipose tissues and their influence on cardiovascular disease: basic mechanisms and clinical associations. *J Am Heart Assoc* 2014; **3**: e000582. doi: <https://doi.org/10.1161/JAHA.113.000582>
2. Lu MT, Park J, Ghemigian K, Mayrhofer T, Puchner SB, Liu T, et al. Epicardial and paracardial adipose tissue volume and attenuation - Association with high-risk coronary plaque on computed tomographic angiography in the ROMICAT II trial. *Atherosclerosis* 2016; **251**: 47–54. doi: <https://doi.org/10.1016/j.atherosclerosis.2016.05.033>
3. Nichols JH, Samy B, Nasir K, Fox CS, Schulze PC, Bamberg F, et al. Volumetric measurement of pericardial adipose tissue from contrast-enhanced coronary computed tomography angiography: a reproducibility study. *J Cardiovasc Comput Tomogr* 2008; **2**: 288–95. doi: <https://doi.org/10.1016/j.jcct.2008.08.008>
4. Mahabadi AA, Massaro JM, Rosito GA, Levy D, Murabito JM, Wolf PA, et al. Association of pericardial fat, intrathoracic fat, and visceral abdominal fat with cardiovascular disease burden: the Framingham heart study. *Eur Heart J* 2009; **30**: 850–6. doi: <https://doi.org/10.1093/eurheartj/ehn573>
5. Sacks HS, Fain JN. Human epicardial adipose tissue: a review. *Am Heart J* 2007; **153**: 907–17. doi: <https://doi.org/10.1016/j.ahj.2007.03.019>
6. Chaldakov GN, Beltowsky J, Ghenev PI, Fiore M, Panayotov P, Rančić G, et al. Adipoparacrinology--vascular periadventitial adipose tissue (tunica adiposa) as an example. *Cell Biol Int* 2012; **36**: 327–30. doi: <https://doi.org/10.1042/CBI20110422>
7. Williams JK, Heistad DD. Structure and function of vasa vasorum. *Trends Cardiovasc Med* 1996; **6**: 53–7. doi: [https://doi.org/10.1016/1050-1738\(96\)00008-4](https://doi.org/10.1016/1050-1738(96)00008-4)
8. Moulton KS, Vakili K, Zurakowski D, Soliman M, Butterfield C, Sylvan E, et al. Inhibition of plaque neovascularization reduces macrophage accumulation and progression of advanced atherosclerosis. **100**. USA: Proc Natl Acad Sci; 2003. pp. 4736–41.
9. Inoue F, Sato Y, Matsumoto N, Tani S, Uchiyama T. Evaluation of plaque texture by means of multislice computed tomography in patients with acute coronary syndrome and stable angina. *Circ J* 2004; **68**: 840–4. doi: <https://doi.org/10.1253/circj.68.840>
10. Rajani R, Shmilovich H, Nakazato R, Nakanishi R, Otaki Y, Cheng VY, et al. Relationship of epicardial fat volume to coronary plaque, severe coronary stenosis, and high-risk coronary plaque features assessed by coronary CT angiography. *J Cardiovasc Comput Tomogr* 2013; **7**: 125–32. doi: <https://doi.org/10.1016/j.jcct.2013.02.003>
11. Sarin S, Wenger C, Marwaha A, Qureshi A, Go BDM, Woomert CA, et al. Clinical significance of epicardial fat measured using cardiac multislice computed tomography. *Am J Cardiol* 2008; **102**: 767–71. doi: <https://doi.org/10.1016/j.amjcard.2008.04.058>
12. Iwasaki K, Matsumoto T, Aono H, Furukawa H, Samukawa M. Relationship between epicardial fat measured by 64-multidetector computed tomography and coronary artery disease. *Clin Cardiol* 2011; **34**: 166–71. doi: <https://doi.org/10.1002/clc.20840>
13. Ueno K, Anzai T, Jinzaki M, Yamada M, Jo Y, Maekawa Y, et al. Increased epicardial fat volume quantified by 64-multidetector computed tomography is associated with coronary atherosclerosis and totally occlusive lesions. *Circ J* 2009; **73**: 1927–33. doi: <https://doi.org/10.1253/circj.CJ-09-0266>
14. Bucci M, Joutsiniemi E, Saraste A, Kajander S, Ukkonen H, Saraste M, et al. Intrapericardial, but not extrapericardial, fat is an independent predictor of impaired hyperemic coronary perfusion in coronary artery disease. *Arterioscler Thromb Vasc Biol* 2011; **31**: 211–8. doi: <https://doi.org/10.1161/ATVBAHA.110.213827>
15. Tanami Y, Jinzaki M, Kishi S, Matheson M, Vavere AL, Rochitte CE, et al. Lack of association between epicardial fat volume and extent of coronary artery calcification, severity of coronary artery disease, or presence of myocardial perfusion abnormalities in a diverse, symptomatic patient population: results from the CORE320 multicenter study. *Circ Cardiovasc Imaging* 2015; **8**: e002676. doi: <https://doi.org/10.1161/CIRCIMAGING.114.002676>
16. Djaberi R, Schuijff JD, van Werkhoven JM, Nucifora G, Jukema JW, Bax JJ. Relation of epicardial adipose tissue to coronary atherosclerosis. *Am J Cardiol* 2008; **102**: 1602–7. doi: <https://doi.org/10.1016/j.amjcard.2008.08.010>
17. Versteysen MO, Takx RAP, Joosen IAPG, Nelemans PJ, Das M, Crijns HJGM, et al. Epicardial adipose tissue volume as a predictor for coronary artery disease in diabetic, impaired fasting glucose, and non-diabetic patients presenting with chest pain. *Eur Heart J Cardiovasc Imaging* 2012; **13**: 517–23. doi: <https://doi.org/10.1093/ehjci/jes024>
18. Sacks HS, Fain JN. Human epicardial fat: what is new and what is missing? *Clin Exp Pharmacol Physiol* 2011; **38**: 879–87. doi: <https://doi.org/10.1111/j.1440-1681.2011.05601.x>
19. Franssens BT, Nathoe HM, Leiner T, van der Graaf Y, Visseren FL, group Sstudy, SMART study group. Relation between cardiovascular disease risk factors and epicardial adipose tissue density on cardiac computed tomography in patients at high risk of cardiovascular events. *Eur J Prev Cardiol* 2017; **24**: 660–70. doi: <https://doi.org/10.1177/2047487316679524>
20. Gifford A, Towse TF, Walker RC, Avison MJ, Welch EB. Characterizing active and inactive brown adipose tissue in adult humans using PET-CT and MR imaging. *Am J Physiol Endocrinol Metab* 2016; **311**: E95–104. doi: <https://doi.org/10.1152/ajpendo.00482.2015>
21. Liu Z, Wang S, Wang Y, Zhou N, Shu J, Stamm C, et al. Association of epicardial adipose tissue attenuation with coronary atherosclerosis in patients with a high risk of coronary artery disease. *Atherosclerosis* 2019; **284**: 230–6. doi: <https://doi.org/10.1016/j.atherosclerosis.2019.01.033>
22. Alvey NJ, Pedley A, Rosenquist KJ, Massaro JM, O'Donnell CJ, Hoffmann U, et al. Association of fat density with subclinical

- atherosclerosis. *J Am Heart Assoc* 2014;; 3: e00078828 Aug 201428. doi: <https://doi.org/10.1161/JAHA.114.000788>
23. Rosenquist KJ, Pedley A, Massaro JM, Theriksen KE, Murabito JM, Hoffmann U, et al. Visceral and subcutaneous fat quality and cardiometabolic risk. *JACC Cardiovasc Imaging* 2013; 6: 762–71. doi: <https://doi.org/10.1016/j.jcmg.2012.11.021>
 24. Zhou J, Chen Y, Zhang Y, Wang H, Tan Y, Liu Y, et al. Epicardial fat volume improves the prediction of obstructive coronary artery disease above traditional risk factors and coronary calcium score. *Circ Cardiovasc Imaging* 2019; 12: e008002. doi: <https://doi.org/10.1161/CIRCIMAGING.118.008002>
 25. Mohar DS, Salcedo J, Hoang KC, Kumar S, Saremi F, Erande AS, et al. Epicardial adipose tissue volume as a marker of coronary artery disease severity in patients with diabetes independent of coronary artery calcium: findings from the CTRAD study. *Diabetes Res Clin Pract* 2014; 106: 228–35. doi: <https://doi.org/10.1016/j.diabres.2014.08.021>
 26. Yerramasu A, Dey D, Venuraju S, Anand DV, Atwal S, Corder R, et al. Increased volume of epicardial fat is an independent risk factor for accelerated progression of sub-clinical coronary atherosclerosis. *Atherosclerosis* 2012; 220: 223–30. doi: <https://doi.org/10.1016/j.atherosclerosis.2011.09.041>
 27. Wheeler GL, Shi R, Beck SR, Langefeld CD, Lenchik L, Wagenknecht LE, et al. Pericardial and visceral adipose tissues measured volumetrically with computed tomography are highly associated in type 2 diabetic families. *Invest Radiol* 2005; 40: 97–101. doi: <https://doi.org/10.1097/00004424-200502000-00007>
 28. Goeller M, Achenbach S, Marwan M, Doris MK, Cadet S, Commandeur F, et al. Epicardial adipose tissue density and volume are related to subclinical atherosclerosis, inflammation and major adverse cardiac events in asymptomatic subjects. *J Cardiovasc Comput Tomogr* 2018; 12: 67–73. doi: <https://doi.org/10.1016/j.jcct.2017.11.007>
 29. Shimabukuro M, Hirata Y, Tabata M, Dagvasumberel M, Sato H, Kurobe H, et al. Epicardial adipose tissue volume and adipocytokine imbalance are strongly linked to human coronary atherosclerosis. *Arterioscler Thromb Vasc Biol* 2013; 33: 1077–84. doi: <https://doi.org/10.1161/ATVBAHA.112.300829>
 30. Mazurek T, Zhang L, Zalewski A, Mannion JD, Diehl JT, Arafat H, et al. Human epicardial adipose tissue is a source of inflammatory mediators. *Circulation* 2003; 108: 2460–6. doi: <https://doi.org/10.1161/01.CIR.0000099542.57313.C5>
 31. Vianello E, Dozio E, Arnaboldi F, Marazzi MG, Martinelli C, Lamont J, et al. Epicardial adipocyte hypertrophy: association with M1-polarization and Toll-like receptor pathways in coronary artery disease patients. *Nutr Metab Cardiovasc Dis* 2016; 26: 246–53. doi: <https://doi.org/10.1016/j.numecd.2015.12.005>
 32. Muir LA, Neeley CK, Meyer KA, Baker NA, Brosius AM, Washabaugh AR, et al. Adipose tissue fibrosis, hypertrophy, and hyperplasia: correlations with diabetes in human obesity. *Obesity* 2016; 24: 597–605. doi: <https://doi.org/10.1002/oby.21377>
 33. Aldiss P, Davies G, Woods R, Budge H, Sacks HS, Symonds ME, et al. 'Browning' the cardiac and peri-vascular adipose tissues to modulate cardiovascular risk. *Int J Cardiol* 2017; 228: 265–74. doi: <https://doi.org/10.1016/j.ijcard.2016.11.074>
 34. Sun K, Kusminski CM, Scherer PE. Adipose tissue remodeling and obesity. *J Clin Invest* 2011; 121: 2094–101. doi: <https://doi.org/10.1172/JCI45887>
 35. Hanley C, Shields KJ, Matthews KA, Brooks MM, Janssen I, Budoff MJ, et al. Associations of cardiovascular fat radiodensity and vascular calcification in midlife women: the Swan cardiovascular fat ancillary study. *Atherosclerosis* 2018; 279: 114–21. doi: <https://doi.org/10.1016/j.atherosclerosis.2018.09.001>
 36. Pracon R, Kruk M, Kepka C, Pregowski J, Opolski MP, Dzielinska Z, et al. Epicardial adipose tissue radiodensity is independently related to coronary atherosclerosis. A multidetector computed tomography study. *Circ J* 2011; 75: 391–7. doi: <https://doi.org/10.1253/circj.cj-10-0441>
 37. Arbab-Zadeh A, Nakano M, Virmani R, Fuster V. Acute coronary events. *Circulation* 2012; 125: 1147–56. doi: <https://doi.org/10.1161/CIRCULATIONAHA.111.047431>
 38. Mahabadi AA, Balcer B, Dykun I, Forsting M, Schlosser T, Heusch G, et al. Cardiac computed tomography-derived epicardial fat volume and attenuation independently distinguish patients with and without myocardial infarction. *PLoS One* 2017; 12: e0183514. doi: <https://doi.org/10.1371/journal.pone.0183514>
 39. Mancio J, Azevedo D, Saraiva F, Azevedo AI, Pires-Morais G, Leite-Moreira A, et al. Epicardial adipose tissue volume assessed by computed tomography and coronary artery disease: a systematic review and meta-analysis. *Eur Heart J Cardiovasc Imaging* 2018; 19: 490–7. doi: <https://doi.org/10.1093/ehjci/jex314>
 40. Mahabadi AA, Berg MH, Lehmann N, Kalsch H, Bauer M, Kara K, et al. Association of epicardial fat with cardiovascular risk factors and incident myocardial infarction in the general population: the Heinz Nixdorf recall study. *J Am Coll Cardiol* 2013; 61: 1388–95. doi: <https://doi.org/10.1016/j.jacc.2012.11.062>