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FULL PAPER

Quantification of epicardial adipose tissue in coronary calcium score and CT coronary angiography image data sets: comparison of attenuation values, thickness and volumes

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Objective: The aim of the study was to compare epicardial adipose tissue (EAT) characteristics assessed with coronary calcium score (CS) and CT coronary angiography (CTCA) image data sets.

Methods: In 76 patients (mean age 59 ± 13 years) who underwent CS and CTCA owing to suspected coronary artery disease (CAD), EAT was quantified in terms of density (Hounsfield units), thickness and volume. The EAT volume was extracted with a semi-automatic software.

Results: A moderate correlation was found between EAT density in CS and CTCA image data sets (-100 ± 19 HU vs -70 ± 24 HU; $p < 0.05$, $r = 0.55$). The distribution of EAT was not symmetrical with a maximal thickness at the right atrioventricular groove (14.2 ± 5.3 mm in CS, 15.7 ± 5 mm

in CTCA; $p > 0.05$, $r = 0.76$). The EAT volume resulted as 122 ± 50 cm³ in CS and 86 ± 40 cm³ in CTCA ($\Delta = 30\%$, $p < 0.05$, $r = 0.92$). After adjustment for post-contrast EAT attenuation difference ($\Delta = 30$ HU), the volume was 101 ± 47 cm³ ($\Delta = 17\%$, $p < 0.05$, $r = 0.92$). Based on EAT volume median values, no differences were found between groups with smaller and larger volumes in terms of Agatston score and CAD severity.

Conclusion: CS and CTCA image data sets may be equally employed for EAT assessment; however, an underestimation of volume is found with the latter acquisition even after post-contrast attenuation adjustment.

Advances in knowledge: EAT may be measured by processing either the CS or CTCA image data sets.

INTRODUCTION

The epicardial adipose tissue (EAT) is a deposit of visceral intrathoracic fat located within the pericardium. EAT surrounds the coronary arteries for most of their anatomic path.¹

Recent articles have shown that EAT may contribute to the development of coronary atherosclerosis owing to the local production of pro-inflammatory cytokines with paracrine effect.^{2–6} Therefore, the distribution of EAT in humans may also contribute to an unfavourable cardiovascular risk profile.⁷ Several studies have proposed methods to measure the EAT characteristics with non-invasive imaging techniques, demonstrating an association with coronary artery disease (CAD),^{8,9} myocardial ischaemia,^{10,11} atrial fibrillation¹² and major adverse cardiovascular events.¹³ EAT has been assessed with echocardiography, MRI and CT using

computer applications.^{14–19} Calcium score (CS) and CT coronary angiography (CTCA) may be employed separately, according to clinical indications with radiation dose reduction.²⁰

The aim of our study was to provide a systematic comparison of density values, thickness and volume, extracted from CS and CTCA image data sets in a cohort of patients with suspected CAD.

METHODS AND MATERIALS

Patients

76 consecutive patients (53 males, mean age 58 ± 13 years, and 23 females, mean age 59 ± 13 years) who underwent both CS and CTCA at our institution between March 2012 and June 2012 for suspected CAD were included in the study. Population characteristics are summarized in Table 1.

The exclusion criteria were: severe renal impairment (creatininaemia $>120 \text{ mmol l}^{-1}$), known allergy to iodinated contrast media, pregnancy, respiratory failure, known CAD including revascularizations with percutaneous interventions and coronary artery bypass grafting and atrial fibrillation. Institutional review board approval and written informed consent were not required, since retrospective data of standard cardiac CT examinations were used.

Scan and reconstruction parameters

Examinations were performed with a 128-slice CT scanner (SOMATOM® Definition AS, Siemens Healthcare, Forchheim, Germany). Firstly, CS was acquired with a standard protocol (120 kV; slice thickness 3 mm, prospective gating). Then, CTCA scans were performed with the following parameters: slice/collimation $64 \times 2/0.6 \text{ mm}$, with z-flying focal spot technique; rotation time 300 ms, effective temporal resolution (with 180° algorithm) 150 ms; 120 kV; 160 mAs per rotation; pitch 0.22; table feed 28.2 mm s^{-1} , field of view 140–180 mm from the carina to the diaphragm; retrospective electrocardiogram gating with prospective modulation of the dose.

All patients with a heart rate of >65 beats per minute (without known contraindications to β -blockers such as asthma, bronchospasm and systolic blood pressure $<100 \text{ mmHg}$) were given a dose of 20–40 mg of propranolol orally 1 h prior to the scan or a 5-mg i.v. dose of atenolol prior to the examinations to lower the heart rate.

A bolus of 80 ml of non-ionic iodinated contrast agent (iomeprol) (Iomeron 400 mgI ml^{-1} ; Bracco, Milan, Italy) was administered at an injection rate of 5 ml s^{-1} using a dual-head

power automatic injector (Stellant®; MedRAD®, Pittsburgh, PA) connected to an 18-gauge needle cannula placed in the right antecubital vein. The iodine delivery rate (IDR) was 2000 mgI s^{-1} for each patient. Saline flushing of 40 ml was administered. Intracoronary enhancement was optimized by using the bolus-tracking technique. A region of interest (ROI) was placed at the level of the ascending aorta in order to synchronize the beginning of the scan with the arrival of the contrast agent in the scan target. The scan started automatically with a 7-s delay after a threshold of 110 HU was reached within the ROI.

Image data sets were reconstructed with an effective slice thickness of 0.75 mm, increment of 0.4 mm and standard smooth convolution filter. Temporal windows with the best image quality were chosen with the motion-mapping technique (BestPhase, Siemens Healthcare) in the telediastolic or in telesystolic phase or in additional phases according to operator experience.

Image analysis

The examinations were evaluated by two radiologists with 10 years' in cardiac CT (LLG and MM), who transferred the image data sets to a workstation (Leonardo, Siemens Healthcare) equipped with dedicated software for post-processing (Syngo Via Cardiac, Siemens Healthcare). Coronary calcifications were defined on CT images as the presence of >2 contiguous pixels with density $>130 \text{ HU}$. These lesions were automatically identified and marked in terms of colour at the workstation. The coronary calcium of each patient was quantified using the Agatston, mass and volume methods.

The Agatston score is obtained by multiplying the area of calcification with its maximum attenuation.²¹

Data from CTCA scans were analyzed with the following post-processing techniques: multiplanar reconstructions, curved multiplanar reconstructions, maximum intensity projections and volume rendering.

Quantification of epicardial adipose tissue

The EAT is defined as the deposit of the visceral intrathoracic adipose tissue within the pericardium and surrounding coronary arteries.¹ EAT was assessed in CS and CTCA data sets in terms of density values (Hounsfield units), thickness (mm) and volume (cm^3). Attenuation values of EAT were measured by tracing a constant ROI of 20 mm^2 in the following anatomic regions: anterosuperior mediastinum at the level of the pulmonary trunk; close to the proximal right coronary artery, left main trunk, proximal left anterior descending artery and proximal circumflex artery; and posterior mediastinum. In addition, a ROI was placed in the subcutaneous fat of the anterior chest wall. We calculated the IDR per kilogram (kg) of individual body weight in order to assess the precise effect of contrast enhancement in a quantifiable manner. We assessed the milligram per kg per second iodine given to each patient in relation to individual arterial enhancement of the aorta (difference between pre- and post-contrast enhancement) and epicardial fat volume (difference between pre- and post-contrast enhancement).

Table 1. Baseline characteristics

Age (years) (mean $\pm$ SD)	59 $\pm$ 13
Male (%)	53 (70%)
BMI (kg m^{-2})	28 $\pm$ 5
Family history (%)	32 (42)
Smoking (%)	18 (24)
Hypertension (%)	51 (67)
Dyslipidemia (%)	31 (41)
Obesity (BMI > 30) (%)	25 (34)
Diabetes (%)	20 (26)
Heart rate (bpm)	61 $\pm$ 8
Agatston calcium score	142 $\pm$ 313
Mass calcium score (mg)	26 $\pm$ 57
Volume calcium score (mm^3)	133 $\pm$ 290
Normal coronary arteries (%)	32 (42)
Not obstructive CAD (%)	29 (38)
Obstructive CAD (%)	15 (20)

BMI, body mass index; bpm, beats per minute; CAD, coronary artery disease; SD, standard deviation.

Maximal thickness was measured from the myocardial wall to the pericardium.¹⁹ Measurements of thickness were performed in a standard horizontal long-axis plane (right atrioventricular groove, anterior interventricular groove and left atrioventricular groove) in the basal short-axis plane (superior and inferior interventricular grooves) and over the right ventricular free wall at three equally spaced points to obtain an average.¹⁹ Thoracic subcutaneous fat was measured anteriorly to the sternum at the four-chamber heart view level. All the measurements were performed at the same point both on the CS and CTCA image data sets in consensus by two radiologists.

A dedicated OsiriX plug-in was developed to calculate the EAT volume. The range of attenuation for EAT segmentation was set

between -30 and -190 HU.¹⁹ The image processing started at the level of the pulmonary trunk and ended at the level of the inferior diaphragmatic surface of the heart. The operator manually drew the pericardial contours every 15 mm (5 slices in CS and 20 slices in CTCA image data set, respectively). Then, the plug-in automatically generated the missing contours by interpolating the image samples (Figure 1). In the end, images were checked and reviewed by operators to correct potential errors. The volume was measured in cubic centimetres on both the CS and CTCA data sets. The voxels with attenuation values in the range of the adipose tissue were multiplied for pixel spacing of the digital imaging and communications in medicine header file. Based on the difference of post-contrast

Figure 1. Examples of pericardial tracing generated with the plug-in in the calcium score and in CT coronary angiography images (a, b) and three-dimensional models as reference images of the isolated epicardial adipose tissue (c, d).

Figure 2. Correlation between iodine delivery rate per kilogram (kg) of patient body weight and aortic enhancement. HU, Hounsfield units; mgl, milligram iodine; s, seconds.

EAT attenuation, a correction of density range was applied to the plug-in extraction, in order to obtain an adjusted volume. The CTCA image data set based on the adjustment for density range was defined as CTCA-A.

Statistical analysis

Data were presented as means $\pm$ standard deviations. Statistical evaluation was performed with dedicated software (SPSS 11.5; IBM Corp., New York, NY; formerly SPSS® Inc., Chicago, IL). Paired attenuation values, thickness and volume of CS and CTCA image data sets, even after adjustment of the density range (data set CTCA-A), were compared with the Student's *t* test or with the one-way analysis of variance and were correlated with the Pearson's test. EAT volumes were grouped according to the median value; the severity of disease in terms of Agatston CS, absolute or by risk category (0, 1–100, 101–400 and >401), and CAD presence at CTCA (normal, $<50\%$ stenosis and $\geq 50\%$ stenosis) were compared with Student's *t* test or with χ^2 analysis. A *p*-value of <0.05 was set for statistical significance.

Figure 3. Correlation between iodine delivery rate per kilogram (kg) of patient body weight and epicardial adipose tissue enhancement. HU, Hounsfield units; mgl, milligram iodine; s, seconds.

RESULTS

38 (34.5%) patients in our population presented an Agatston CS of 0. The mean Agatston CS was 142 ± 313 (16 patients with score 1–100, 12 patients with score 101–400 and 10 patients with score >400). The mean mass and volume scores were 26 ± 57 mg and 133 ± 290 mm³, respectively. 32 (42%) patients with suspected CAD had normal coronary arteries at CTCA. 29 (38%) patients did not have obstructive CAD, and 15 (20%) patients had obstructive CAD at CTCA.

The increment of aortic enhancement (429 ± 97 HU) was 11.3 times with respect to baseline (38 ± 11 HU) and its correlation with IDR per kg of patient body weight was moderate ($r = 0.53$) (Figure 2). Mean attenuation values of EAT were higher in CTCA image data sets than in CS data sets, with greater difference in mediastinal and juxtacoronary measurements than that in the subcutaneous fat of the anterior chest wall ($p < 0.05$) (Table 2). A moderate correlation was found between overall mean attenuation values of EAT in CS and CTCA (-100 ± 19 HU vs -70 ± 24 HU; $p < 0.05$, $r = 0.55$). The increment of epicardial fat enhancement was just 0.7 times during the arterial

Table 2. Comparison between adipose tissue attenuation values in calcium score (CS) and CT coronary angiography (CTCA) image data sets

Measurement of the adipose tissue	Mean HU $\pm$ SD in CS data set	Mean HU $\pm$ SD in CTCA data set	Δ (HU)	<i>p</i> -value	<i>r</i>
Anterosuperior mediastinum	-98 ± 16	-76 ± 23	22	<0.05	0.58
Close to RCA	-97 ± 16	-66 ± 22	31	<0.05	0.44
Close to LM	-97 ± 16	-66 ± 27	31	<0.05	0.42
Close to LAD	-99 ± 16	-68 ± 19	31	<0.05	0.56
Close to CX	-98 ± 18	-66 ± 20	32	<0.05	0.47
Posterior mediastinum	-109 ± 26	-77 ± 28	32	<0.05	0.69
Overall epicardial	-100 ± 19	-70 ± 24	30	<0.05	0.55
Anterior chest wall	-104 ± 14	-92 ± 18	12	<0.05	0.72

CX, circumflex artery; HU, Hounsfield units; LAD, left anterior descending artery; LM, left main trunk; *r*, Pearson's correlation coefficient; RCA, right coronary artery; SD, standard deviations.

Table 3. Comparison between epicardial adipose tissue thickness in calcium score (CS) and CT coronary angiography (CTCA) image data sets

Thickness	Mean $\pm$ SD (mm) in CS data set	Mean $\pm$ SD (mm) in CTCA data set	Δ (mm)	<i>p</i> -value	<i>r</i>
Right atrioventricular groove	14.2 $\pm$ 5.3	15.7 $\pm$ 5	1.5	>0.05	0.76
Anterior interventricular groove	6.6 $\pm$ 2.5	7.2 $\pm$ 2.9	0.6	>0.05	0.86
Left atrioventricular groove	10.6 $\pm$ 2.9	10.7 $\pm$ 2.8	0.1	>0.05	0.73
Superior interventricular groove	11.8 $\pm$ 3.7	12.1 $\pm$ 3.5	0.3	>0.05	0.76
Inferior interventricular groove	5.6 $\pm$ 2	5.4 $\pm$ 1.7	0.2	>0.05	0.78
Overall grooved	10.1 $\pm$ 2.3	10.2 $\pm$ 2.4	0.1	>0.05	0.88
Right ventricular free wall	5.6 $\pm$ 2.6	5.9 $\pm$ 2.9	0.3	>0.05	0.88
Thoracic subcutaneous fat	17.4 $\pm$ 8	17.5 $\pm$ 8	0.1	>0.05	0.99

r, Pearson's correlation coefficient; SD, standard deviation.

phase with respect to baseline, and its correlation with IDR per kg of patient body weight was low ($r = 0.11$) (Figure 3).

The distribution of EAT was not symmetrical, with a maximal thickness at the right atrioventricular groove (14.2 $\pm$ 5.3 mm in CS and 15.7 $\pm$ 5 mm in CTCA) (Table 3). The thickness of the grooved segments (10.1 $\pm$ 2.3 mm in CS and 10.2 $\pm$ 2.4 mm in CTCA) was greater ($p < 0.05$) than that of the right ventricular free wall (5.7 $\pm$ 2.6 mm in CS and 5.9 $\pm$ 2.9 mm in CTCA). No differences were found between the thickness measured in CS and CTCA image data sets ($p > 0.05$). A high correlation was found between the thickness measured in CS and CTCA with reference to the right ventricular free wall ($r = 0.88$) and the mean of the grooved segments ($r = 0.88$).

The EAT volume in the CS data set was 122 $\pm$ 50 cm³, whereas the volume in the CTCA data set was 86 $\pm$ 40 cm³ ($p < 0.05$, $r = 0.92$) (Figure 4). Time processing of volumes slightly differed

between CS and CTCA image data sets (5 $\pm$ 1 vs 7 $\pm$ 2 min; $p < 0.05$). After adjustment for the post-contrast EAT attenuation difference ($\Delta = 30$ HU, density range set from -175 to -15 HU), the volume resulted as 101 $\pm$ 47 cm³ ($p < 0.05$, $r = 0.92$) (Figure 5). Even though it was low and occurred early, as discussed above, EAT enhancement determined a reduction of post-contrast volume ($\Delta = 30\%$), also after adjustment of the density range ($\Delta = 17\%$).

EAT volumes were weakly correlated with age ($r = 0.35$ in CS, $r = 0.32$ in CTCA and $r = 0.29$ in CTCA-A) and body mass index ($r = 0.38$ in CS, $r = 0.27$ in CTCA and $r = 0.26$ in CTCA-A). Males presented a larger EAT volume than females (CS: 128 $\pm$ 53 cm³ vs 108 $\pm$ 40 cm³, $p > 0.05$; CTCA: 94 $\pm$ 43 cm³ vs 69 $\pm$ 28 cm³, $p < 0.05$; and CTCA-A: 110 $\pm$ 51 cm³ vs 82 $\pm$ 31 cm³, $p < 0.05$).

Although not significant, patients with an Agatston score of 0 had a smaller EAT volume than patients with an Agatston score $\neq 0$ (118 $\pm$ 53 cm³ vs 126 $\pm$ 48 cm³ for the CS data set, $p > 0.05$; 79 $\pm$ 37 cm³ vs 93 $\pm$ 43 cm³ for the CTCA data set, $p > 0.05$; and 95 $\pm$ 48 cm³ vs 108 $\pm$ 47 cm³ for CTCA-A, $p > 0.05$).

The population was divided into two subgroups according to the median EAT volume (smaller and larger than median values: 112 cm³ in the CS data set, 77.5 cm³ in the CTCA data set and 89.5 cm³ in CTCA-A, respectively). No differences were found between groups with smaller and larger EAT volumes in terms of Agatston score, absolute or by risk category, and CAD severity (Table 4).

DISCUSSION

According to literature, EAT differs from other adipose tissues because of its specific anatomic, histological and biochemical pattern.^{4,16,19} EAT may contribute to the progression of coronary atherosclerosis owing to the onsite production of pro-inflammatory cytokines.²⁻⁷ Non-invasive imaging techniques such as echocardiography, MRI and CT may reliably quantify

Figure 4. Correlation between the epicardial adipose tissue volume processed in calcium score (CS) and CT coronary angiography (CTCA) image data sets. *r*, Pearson's correlation coefficient.

Table 4. Comparison of groups divided according to the median values of epicardial adipose tissue volume

Disease parameter	CS data set		CTCA		CTCA-A	
EAT volume	<111.5 cm ³	>111.5 cm ³	<77.5 cm ³	>77.5 cm ³	<89.5 cm ³	>89.5 cm ³
CS value	126 ± 310	158 ± 321	128 ± 316	156 ± 314	119 ± 312	165 ± 317
CS = 0 (%)	20 (52.7)	18 (47.4)	20 (52.7)	18 (47.4)	20 (52.7)	18 (47.4)
CS, 1–100 (%)	9 (23.7)	7 (18.4)	10 (26.3)	6 (15.8)	11 (28.9)	5 (13.1)
CS, 101–400 (%)	5 (13.1)	7 (18.4)	3 (7.9)	9 (23.7)	3 (7.9)	9 (23.7)
CS > 401 (%)	4 (10.5)	6 (15.8)	5 (13.1)	5 (13.1)	4 (10.5)	6 (15.8)
No CAD	15 (39.5)	17 (44.7)	15 (39.5)	17 (44.7)	15 (39.5)	17 (44.7)
CAD < 50% (%)	17 (44.7)	12 (31.6)	16 (42.1)	13 (34.2)	17 (44.7)	12 (31.6)
CAD > 50% (%)	6 (15.8)	9 (23.7)	7 (18.4)	8 (21.1)	6 (15.8)	9 (23.7)

CAD, coronary artery disease; CS, calcium score; CTCA, CT coronary angiography; CTCA-A, CTCA image data set based on adjustment for density range.

$p > 0.05$ was found for absolute Agatston CS value, risk categories of CS and CAD severity, according to CTCA findings.

the distribution and volume of EAT.^{8–11,14–16} In particular, cardiac CT may simultaneously provide the evaluation of CAD findings and EAT in a non-invasive manner.^{15–20} Computer applications may be used to select, process and quantify EAT, based on the known adipose tissue attenuation range in image data sets. Typically, the attenuation limits for EAT are identified from –250 to –190 HU for the lower limit and from –50 to –30 HU for the upper limit.^{19,22,23} In our study, we analyzed the relationship between EAT measurements in CS and CTCA image data sets. Our study confirms a systematic underestimation of EAT volume ($\Delta = 30\%$) in CTCA owing to contrast media enhancement. Therefore, we suggested a modified range between –175 and –15 HU, based on the attenuation difference between baseline and post-contrast values of EAT ($\Delta = 30$ HU), to mitigate the underestimation of volume ($\Delta = 17\%$). Nonetheless, the contrast enhancement of EAT may be influenced by contrast media choice and individual factors such as ejection fraction.^{24,25}

According to literature, the time processing of EAT volume extracted from image data sets is small.^{8–13} The distribution of EAT is not symmetrical and uniform, and it is prevalent at

grooved segments for both data sets^{1,26} (Figures 6 and 7). The thickness of EAT at the left atrioventricular groove is reported to be predictive of atherogenic risk, even more than the total volume.^{22,27} Mahabadi et al demonstrated that the thickness of EAT is often associated with the presence of atherosclerotic plaques in the proximal grooved coronary segments, although these regions of the coronary tree typically show the first signs of atherosclerosis, with a possible overlapping effect.¹ On the other side,

Figure 6. Example of pericoronary fat (arrow) adjacent to a stenotic lesion (arrowheads) of the mid-right coronary artery (RCA): horizontal long-axis plane (a), basal short-axis plane (b), volume rendering (c) and multiplanar reconstruction of the RCA (d). The stenosis of the mid-RCA is associated with the maximal epicardial adipose tissue (EAT) thickness (double-headed arrow, a) of the right atrioventricular groove (20 mm), while EAT thickness over the right ventricular free wall (double-headed arrow, b) and the volume are average (8 mm and 81 cm³, respectively).

Figure 5. Correlation between the epicardial adipose tissue volume processed in calcium score (CS) and CT coronary angiography image data set based on the adjustment for density range (CTCA-A). r , Pearson's correlation coefficient.

Figure 7. Example of pericoronary fat (arrows) adjacent to a stenotic lesion (arrowheads) of the mid-left anterior descending artery (LAD): horizontal long-axis plane in calcium score (a) and CT coronary angiography image data sets (b) and multiplanar reconstructions of the LAD (c, d). The stenosis of the mid-LAD is associated with the maximal epicardial adipose tissue (EAT) thickness of the anterior interventricular groove (10 mm), while EAT volume is average (77 cm³).

the quantification of EAT volume is reported to be more reproducible than the thickness measurement,²⁸ despite the absence of reference values for volume being a limitation for clinical use.¹ Given that CS and CTCA may be used singularly in order to reduce the radiation dose, a systematic comparison of EAT assessment with those two acquisitions is useful to define the interchangeability of the method.

According to literature,^{1,29} EAT volume is weakly correlated with male gender, age and body mass index. It is still controversial whether CS and EAT values are correlated.^{28,30} Bettencourt et al²⁸ demonstrated a linear correlation, while Mahabadi et al³⁰

showed that the association is not significant, but it is influenced by cardiovascular risk factors. According to our study, the volumes of EAT are independent of CS values. Both findings are risk factors of atherosclerosis, but, they probably refer to different pathogenic pathways of CAD.^{23,30,31} The severity of CAD assessed with CTCA is also not affecting EAT volumes, even in case of obstructive disease.^{28,32}

Some limitations occurred in our study. The first is that we did not perform a follow-up of patients. EAT is correlated with the progression of CAD⁹ and major adverse cardiovascular events,

including sudden cardiac death, myocardial infarction, stroke and coronary revascularization.^{1,13,16} However, the primary aim of our study was to compare measurements and quantification of EAT in CS and CTCA image data sets. The second limitation is that our sample did not include patients with acute presentation. The analysis of patients with acute presentation and dysmetabolic syndrome could provide an explanation of the potential association between EAT volume, CS and coronary plaque composition, including non-calcified plaques and positive remodelling.^{13,33–35} The increase of C-reactive protein and the reduction of adiponectin in the adipose tissue may contribute

to the progression of atherosclerosis.³⁶ Atrial fibrillation is also reported to be correlated with EAT volume;³⁷ however, we did not include patients with atrial fibrillation.

CONCLUSION

CS and CTCA image data sets may be equally employed for EAT quantification, but an underestimation of volume is found with the latter acquisition even after post-contrast attenuation adjustment. The assessment of EAT in large population studies should be encouraged to elucidate its pathophysiology and prognostic role in CAD.

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