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ORIGINAL ARTICLE

Clinical usefulness of epicardial adipose tissue in patients with high-intermediate pre-test probability for coronary artery disease

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Abstract

Background: Epicardial adipose tissue (EAT) is thought to be associated with the extension and severity of coronary artery disease (CAD), and echocardiographic measurement of EAT thickness is considered to be a possible cardiovascular risk indicator. The European Society of Cardiology Task Force recommends further non-invasive testing in patients with an intermediate pre-test probability (PTP) for the diagnosis of CAD.

Aim: We sought to evaluate the clinical usefulness of performing EAT measurements in patients with a high-intermediate PTP.

Methods: Patients referred to an outpatient clinic with stable chest pain symptoms, with PTP for CAD between 66% and 85%, were included in the study. Echocardiographic measurement of the EAT was identified as the echo-free space between the outer wall of the myocardium and the visceral layer of the pericardium. Single-photon emission computed tomography (SPECT) was performed in all patients. The diagnosis of CAD was based on the presence of reversible perfusion defects on SPECT.

Results: A total of 126 patients (76 men, 60.3%) with a mean age of 65.3 ± 9.1 years were recruited. The EAT thickness was 7.3 ± 0.7 mm in patients with positive SPECT and 6.2 ± 0.6 mm in patients with negative SPECT ($p < 0.001$). Multivariable analysis revealed higher rates of positive SPECT in patients with higher EAT (odds ratio [OR] 9.80; 95% confidence interval [CI] 3.72–25.79; $p < 0.001$), and receiver operating characteristic curve analysis showed that the greatest specificity was obtained when the cut-off value of EAT thickness was 6.75 mm (sensitivity 76%; specificity 74%).

Conclusions: In patients with high-intermediate PTP, EAT is a useful measurement that may assist in risk stratification.

Key words: echocardiography, epicardial adipose tissue, pre-test probability, single-photon emission computed tomography

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INTRODUCTION

Epicardial adipose tissue (EAT) is an accumulation of true visceral fat surrounding the heart, especially along the major branches of the coronary arteries. EAT directly reflects the deposition of the visceral adipose tissue that is related to a cardiometabolic risk profile. It is an extremely active tissue, rich in free fatty acids, with various secretory functions such as expression of higher levels of pro-atherogenic interleukin 6 mRNA and depletion of anti-atherogenic adiponectin mRNA [1]. Because epicardial fat and myocardium share the same microcirculation, these inflammatory signals are thought to induce atherogenic changes in the coronary arteries by modifying vascular homeostasis, promoting endothelial dysfunction, and aggravating vascular inflammation [2, 3].

Accordingly, epicardial fat is thought to be associated with coronary flow reserve, subclinical atherosclerosis, and exten-

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sion and severity of coronary artery disease (CAD) [4–6]. Thus, echocardiographic measurement of EAT thickness has been considered as a possible indicator of cardiovascular risk [7].

The precise usage of non-invasive cardiac investigations in supporting the diagnosis of CAD can only be established in connection with pre-test probability (PTP). PTP is the clinical possibility that a given patient will develop CAD, based on simple clinical clues, as well as the prevalence of CAD in the assessed population. Also, to achieve post-test probability of CAD for a given patient, pre-test estimates and the results of non-invasive cardiac test should be evaluated together. Inappropriate testing may cause harm because of a higher chance of false test results. Based on the assumption that patients with a low PTP (< 15%) have no obstructive CAD and patients with a high PTP (> 85%) have obstructive CAD, the European Society of Cardiology (ESC) Task Force recommends further non-invasive testing in patients with an intermediate PTP of 15% to 85% [8]. Moreover, guidelines uphold imaging stress test as the initial test for the diagnosis of CAD in patients with a high-intermediate PTP of 66% to 85% [8]. A resting transthoracic echocardiography is also recommended in all patients with a high-intermediate PTP for either diagnostic or risk stratification purposes.

The purpose of this study was to assess the clinical usefulness of echocardiographic EAT measurements in patients with a high-intermediate PTP.

METHODS

Patient population

The study population consisted of patients referred to an outpatient clinic with stable chest pain symptoms. Inclusion criteria comprised PTP between 66% and 85% for stable CAD after clinical assessment on the basis of sex, age, and symptoms [8]. A total of 126 (76 men, 60.3%) consecutive symptomatic patients with no previous history of overt atherosclerotic disease (cerebral, peripheral, or CAD, which was defined as any degree of CAD on previous angiogram or history of myocardial infarction, revascularisation, or angina), heart failure, and renal impairment (creatinine level > 1.4 mg/dL) were recruited. We excluded patients with uncontrolled hypertension, poor echocardiographic imaging, prosthetic heart valve, pericardial effusion, moderate to severe valvular disease, stroke, and unstable angina pectoris. Complete medical history was obtained and detailed physical examination was performed in all patients. Blood pressure was measured in the supine position after 10-min rest. Anthropometric characteristics were measured, and body mass index (BMI) was calculated as weight/height squared (kg/m^2). Blood samples were taken for haematological and biochemical evaluation. Calcium channel blockers and β-blockers, if used, were discontinued for 48 h, and all patients were prepared for myocardial perfusion imaging for evaluation of possible CAD symptoms. Clinical model of PTP was used for CAD in our study population. Informed consent was obtained from all patients, and the investigation conformed to the principles of the Declaration of Helsinki. The study protocol was approved by the Local Ethical Committee.

Myocardial perfusion imaging study

To evaluate the presence of ischaemic heart disease, all patients underwent myocardial perfusion single-photon emission tomography (SPECT) imaging using a one-day gated single isotope 99mTc-sestamibi stress/rest protocol, as suggested in the guidelines [9]. Treadmill ergometry using standard protocols was achieved for stress imaging unless physical exercise was not possible or insufficient. In such case, pharmacological stress test induced with intravenous adenosine (dose of 140 μg/kg per min for 6 min) was used either alone or combined with physical stress. The images at rest and during stress were gathered using a Siemens Multispect 2HD/HD gamma camera (Siemens, Stokesdale, NC, USA). A positive test was defined as the presence of reversible perfusion defects on visual inspection located in any of the myocardial territories during stress.

Echocardiographic measurement

A complete transthoracic echocardiography using a 3.5-MHz transducer (Vivid 7, GE-Vingmed Ultrasound AS, Horten, Norway) was carried out in each patient. EAT was identified as the echo-free space between the outer wall of the myocardium and the visceral layer of the pericardium, and its thickness was measured on the free wall of the right ventricle from the parasternal long- and short-axis views according to the method previously described [10]. The maximum EAT was calculated at the point on the free wall of the right ventricle at end-systole, and measurements were done perpendicularly to the aortic annulus for the parasternal long-axis view and perpendicularly to the interventricular septum at the mid-chordal and tip of the papillary muscles level for the parasternal short-axis view (Fig. 1). The mean value of the two measurements was used to reflect the thickness the EAT. The echocardiograms were performed before the SPECT imaging, and both procedures were performed by the same operator. The average value of three consecutive cardiac cycles from each echocardiographic view was studied. To test the reproducibility of EAT measurement, the measurement was repeated one week later in 20 patients.

Statistical analysis

Categorical and numerical variables are shown as percentage and mean ± standard deviation, respectively. Descriptive statistics was used for definition of clinical and social demographic variables. Kolmogorov-Smirnov test was used to test the normality of the variances. Numerical variables were tested with unpaired Student t test, and categorical variables were tested using χ^2 test. Spearman's test was used for correlation analysis. Receiver operating characteristic (ROC) curve

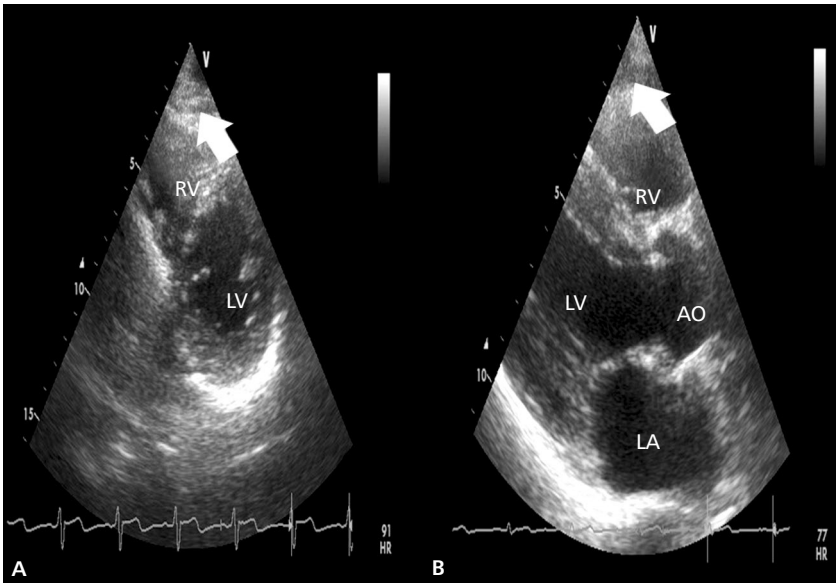

Figure 1. Arrows showing epicardial fat thickness measured by echocardiography in the parasternal short-axis (**A**) and long-axis (**B**) views; AO — aorta; LA — left atrium; LV — left ventricle; RV — right ventricle

analysis was performed to identify the optimal cut-off value of EAT thickness (at which sensitivity and specificity would be maximal) for the prediction of ischaemia-positive SPECT. Sensitivity, specificity, and positive and negative predictive values of the obtained EAT cut-off value for ischaemia-positive SPECT were calculated. Multiple logistic regression analysis using the backward logistical regression method was applied to determine the best predictor(s) that affected mortality after adjustment for all possible confounding factors. Any variable with a p value < 0.25 in a univariate test was accepted as a candidate for a multivariable analysis, along with all variables of known clinical importance. Odds ratios (ORs) and 95% confidence intervals (CIs) for each independent variable were also calculated. A p value < 0.05 was considered significant. All the statistical tests were done using SPSS 16.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

Mean EAT thickness was 6.6 ± 0.8 mm (range 4.8–9.4 mm). The intraobserver, intraclass correlation coefficient for EAT measurement was 0.86. Heredity for CAD was 29% within the study population. A total of 41 patients were using oral anti-diabetics and 22 patients were on insulin treatment. CAD was diagnosed based on SPECT. SPECT was positive for ischaemia in 39 (31.0%) of the 126 patients. Thirteen patients had > 10% inducible ischaemia in SPECT. Exercise SPECT was performed in 46 (36.5%) patients. Patients with pathological results of the perfusion study had a difference in high-density lipoprotein cholesterol and total cholesterol levels, systolic blood pressure, and BMI (Table 1). Among ischaemia-positive patients there was a higher ratio of smokers and patients with hypertension (Table 1). The EAT thickness in patients with ischaemia-positive SPECT was significantly greater than in patients with ischaemia-negative SPECT. The EAT thickness was 7.3 ± 0.7 mm in patients with ischaemia-positive SPECT and 6.2 ± 0.6 mm in patients with ischaemia-negative SPECT ($p < 0.001$) (Fig. 2).

Results of univariate and multivariable analyses are shown in Table 2. Variables with a significant p value in univariate analysis were included into multivariable analysis. According to the results of the multivariable regression analysis, epicardial adipose tissue was an independent predictor (OR 9.80; 95% CI 3.72–25.79; $p < 0.001$) of ischaemia-positive SPECT along with systolic blood pressure (OR 1.01; 95% CI 1.00–1.02; $p = 0.03$) and BMI (OR 1.51; 95% CI 1.13–2.02; $p = 0.005$). The correlations between EAT thickness and waist circumference, BMI, high-density lipoprotein level, systolic blood pressure, heart rate, presence of diabetes mellitus, and inducible ischaemia ratio are presented in Table 3. Correlation analysis of the epicardial adipose tissue and the inducible ischaemia ratio in SPECT was performed by the Spearman's rank correlation test and presented on a scatterplot (ρ: 0.703, $p < 0.001$; Fig. 3). ROC analysis showed that the best cut-off value of the EAT thickness to ischaemia in SPECT was 6.75 mm with 76% sensitivity and 74% specificity (area under curve 0.85; 95% CI 0.78–0.92; $p < 0.001$; Fig. 4).

DISCUSSION

In this study, we prospectively examined the predictive value of echocardiographic EAT for the presence of perfusion defects diagnosed by SPECT in symptomatic patients with high-intermediate (66%–85%) PTP. The EAT in the present study was

Table 1. Characteristics of patients positive and negative for ischaemia in single-photon emission computed tomography (SPECT)

	SPECT ischaemia (–) (n = 87)	SPECT ischaemia (+) (n = 39)	p
Age [years]	65.4 ± 8.8	65.3 ± 10.0	0.950
Male sex	53 (61%)	23 (59%)	0.830
Diabetes mellitus	31 (35%)	18 (46%)	0.260
Hypertension	23 (26%)	20 (51%)	0.007
Smoking	40 (46%)	26 (66%)	0.030
Family history of CAD	24 (27%)	13 (33%)	0.510
Heart rate [bpm]	76.7 ± 8.8	80.1 ± 9.2	0.050
Body mass index [kg/m^2]	30.1 ± 2.6	31.7 ± 2.3	0.002
Systolic blood pressure [mmHg]	121.1 ± 14.4	132.1 ± 12.9	0.010
Diastolic blood pressure [mmHg]	81.5 ± 9.0	82.3 ± 7.9	0.160
Triglyceride [mg/dL]	131.5 ± 43.8	139.2 ± 34.9	0.346
Total cholesterol [mg/dL]	212 ± 56.2	231.2 ± 49.5	0.020
LDL cholesterol [mg/dL]	145.3 ± 38.2	141 ± 27.4	0.380
HDL cholesterol [mg/dL]	39.9 ± 8.6	45.5 ± 8	0.070
Height [cm]	165.9 ± 5.4	168.1 ± 7.0	0.080
Weight [kg]	83.0 ± 7.5	89.7 ± 7.8	0.001
Waist circumference [cm]	90.7 ± 5.2	91.6 ± 6.3	0.370
Ejection fraction [%]	61.2 ± 5.2	60.0 ± 4.0	0.233
Mean EAT [mm]	6.2 ± 0.6	7.3 ± 0.7	< 0.001

Data are shown as mean ± standard deviation or number (percentage). CAD — coronary artery disease; EAT — epicardial adipose tissue; HDL — high-density lipoprotein; LDL — low-density lipoprotein

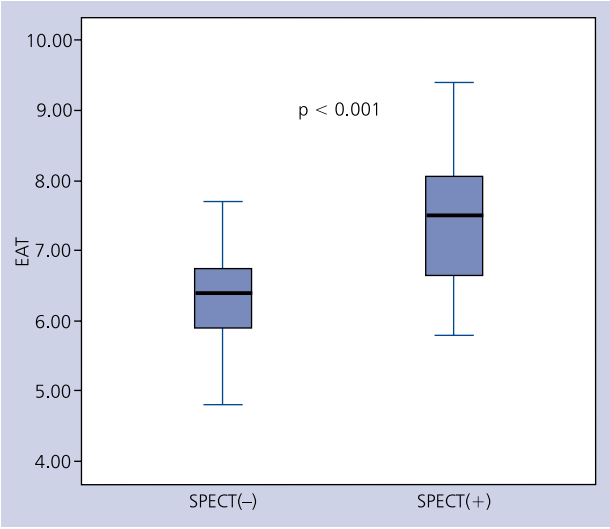

Figure 2. Distribution of the epicardial adipose tissue (EAT) thickness in patients positive and negative for ischaemia in myocardial perfusion imaging study (single-photon emission computed tomography [SPECT], myocardial perfusion imaging study)

greater in the group of patients with ischaemia-positive SPECT. We found EAT measurement to be 7.3 ± 0.7 mm in patients with ischaemia-positive SPECT. Although this finding is in accordance with the literature [11], the range and mean value of EAT found in this study are in fact higher due to higher mean age and higher pre-test probabilities for CAD in the patients, and the fact that documented ischaemia was considered as the outcome. Also, Nelson et al. [5] concluded that a greater burden of EAT measured by echocardiography would identify individuals at increased risk for cardiovascular events, and higher cut-off values of EAT were consistently identified in higher-risk groups within their cohort.

Results of our study are consistent with a previous study [12], which showed that EAT is an independent factor related to the presence of CAD, which is significantly and proportionally increased according to the extent of cardiac fat deposition. Other studies declared that EAT significantly correlated with severe multiple of coronary artery stenosis and identified EAT as a marker of severity of coronary lesions [13, 14]. Measurements of EAT in those studies were done either in patient populations with low PTP, in patients with acute coronary syndrome and/or chronic stable angina referred for coronary angiography, or in patients with an abnormal results of the stress test. However, uniquely, the present study evaluates the EAT in patients with high-intermediate PTP and its relation to the presence of reversible perfusion defects on SPECT.

Table 2. Univariate predictors and multivariable model for ischaemia-positive single-photon emission computed tomography

Univariate analysis	p	Multivariable analysis	p	OR (95% CI)
Height*	0.061			
Weight*	< 0.001			
EAT	< 0.001	EAT	< 0.001	9.80 (3.72–25.79)
HDL	0.001			
Total cholesterol	0.075			
SBP	< 0.001	SBP	0.030	1.01 (1.00–1.02)
Heart rate	0.060			
Ejection fraction	0.230			
Smoking	0.034			
Hyperlipidaemia	0.008			
Hypertension	0.008			
BMI	0.002	BMI	0.005	1.51 (1.13–2.02)

All clinically relevant parameters were included in the model. Only parameters that reached statistical significance in univariate analysis were given in the leftmost column. *These parameters were not included in the multivariable model as they are components of BMI. BMI — body mass index; CI — confidence interval; EAT — epicardial adipose tissue; HDL — high-density lipoprotein; OR — odds ratio; SBP — systolic blood pressure

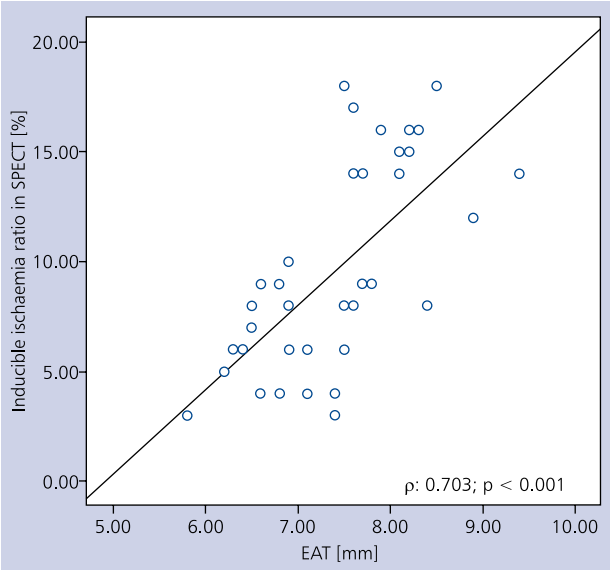

Figure 3. Correlation analysis of the epicardial adipose tissue (EAT) and the inducible ischaemia ratio in single-photon emission computed tomography (SPECT) performed by the Spearman rank correlation test and presented by using scatter dot analysis (ρ: 0.703, p < 0.001)

Table 3. Spearman rank correlation (R) between epicardial adipose tissue (EAT) and waist, body mass index (BMI), high-density lipoprotein (HDL), systolic blood pressure (SBP), heart rate, presence of diabetes mellitus (DM), and inducible ischaemia ratio

Variable	R	p
EAT and waist	0.297	< 0.001
EAT and BMI	0.308	< 0.001
EAT and HDL	0.388	< 0.001
EAT and SBP	0.324	< 0.001
EAT and heart rate	0.300	< 0.001
EAT and presence of DM	0.276	< 0.001
EAT and inducible ischaemia ratio	0.703	< 0.001

Because inflammatory mediators originating outside the coronary artery are capable of promoting compositional changes in the inner layer of intima, EAT produces a local proatherosclerotic effect by means of paracrine and vasocrine secretions of inflammatory adipokines [15, 16]. Age and obesity, by increasing fat mass or fat tissue redistribution to the trunk and viscera, are important determinants of EAT. Although it is found to be related with cardiovascular and metabolic risk factors, as in our study [17], a study by Nelson et al. [5] revealed a weak correlation between EAT and Framingham risk score and no correlation with subclinical atherosclerosis assessed by carotid intima-media thickness, carotid artery plaque, and coronary artery calcium score. However, recently Canpolat et al. [18] clarified that EAT measured by echocardiography independently predicted the AF recurrence after cryoablation and was also positively correlated with high-sensitivity C-reactive protein as an indicator of systemic inflammation. This discrepancy may be due to the different nature of study populations. Also, Ding et al. [19] supported the idea that epicardial fat is a better predictor of incident coronary heart disease than more general measures of adiposity such as BMI or waist circumference.

Furthermore, we investigated the cut-off level of mean EAT for identifying the presence of perfusion defects. In the

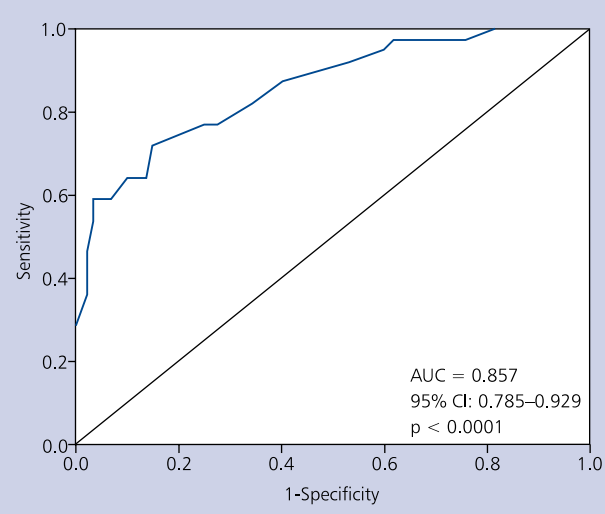

Figure 4. Receiver operating characteristic curve analysis identifying ischaemia-positive myocardial perfusion imaging study. The cut-off value of mean epicardial adipose tissue thickness was set at 6.75 mm; AUC — area under curve; CI — confidence interval

setting of patients with PTP between 66% and 85%, when the cut-off value of mean EAT was set at 6.75 mm, it had 76% sensitivity and 74% specificity for the indication of ischaemia. Mustelier et al. [12] found that EAT ≥ 5.2 mm in systole had 65.4% sensitivity and 61.5% specificity for predicting CAD, and Eroglu et al. [20] found that an EAT thickness of 5.2 mm in diastole had 85% sensitivity and 81% specificity for predicting the presence of CAD in symptomatic subjects undergoing coronary angiography. In those studies the presence of CAD was defined as one or more stenosis ≥ 50% in diameter and ≥ 20% in diameter (for the latter) of a major epicardial vessel. However, we found that an EAT thickness of 6.75 mm in diastole had 76% sensitivity and 74% specificity for the indication of active myocardial ischaemia on nuclear perfusion scanning. Recently, Khawaja et al. [21] demonstrated a selective increase of epicardial fat volume (EFV) measured by computed tomography (CT) in regions of myocardial ischaemia detected by myocardial perfusion imaging; but regions of myocardium with normal perfusion or myocardial scarring were characterised by lower EFV [21]. In addition, Uygur et al. [22] reported that left atrioventricular groove EFV measured by contrast-enhanced CT was an independent predictor of CAD in type 2 diabetic patients without a history of CAD. Recently, Tabakci et al. [23] showed that EAT was inversely correlated with functional status and disease severity in patients with heart failure. Furthermore, EFV assessed by CT was an independent predictor of ischaemia on positron emission tomography in correlation with intermediate PTP of CAD. Also, the EAT preferential increase along non-calcified, vulnerable plaque lesions was compared to chronically calcified coronary lesions [24]. To our knowledge, the present study is the first to show the association between EAT measured by echocardiography and inducible myocardial perfusion. Besides obstructive coronary plaques, EAT may also affect myocardial perfusion by inducing endothelial damage, microvascular dysfunction, and deterioration of coronary flow via exacerbated inflammatory milieu. EAT is consistently associated with CAD, and the incidence of significant coronary artery stenosis increased in proportion to the EAT despite varying methodologies and study populations. In the future, EAT thickness measurements may play an important role in the clinical practice of patients with high-intermediate pre-test probability of CAD. Our results support the role of echocardiographic EAT quantification in risk stratification of patients with high-intermediate PTP.

Our sample size was relatively small and did not include patients with acute coronary syndrome and patients with low PTP. Secondly, echocardiographic measurement may not completely reflect epicardial fat distribution when compared to magnetic resonance imaging or CT because of its three-dimensional distribution. Another limitation of our study is the fact that although we planned to include patients with a pre-test probability of 66% to 85%, only 31% of them had ischaemia-positive SPECT results. This may be due to the dynamic nature of ischaemia detected by SPECT not reflecting silent lesions. Furthermore, absence of universal coronary angiography and coronary flow reserve quantification confined us to validate the asserted mechanisms. Finally, the lack of prospective follow-up is another limitation of our study.

Conflict of interest: *none declared*

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