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Prognostic Value of Epicardial fat Thickness in Coronary Heart Disease Patients After Myocardial Revascularization

Objective	To study the role of epicardial adipose tissue (EAT) in determination of risk for adverse course of ischemic heart disease (IHD) in patients after myocardial revascularization.
Materials and Methods	This study included 217 subjects, 182 IHD patients and 35 evaluated individuals without IHD. Percutaneous coronary intervention (PCI) was performed for 104 patients and coronary bypass (CB) was performed for 78 patients. Also echocardiography (EchoCG) and cardiac computed tomography were performed.
Results	In IHD patients, EAT volume and thickness were greater than in evaluated subjects without IHD. The composite endpoint (CEP) was observed after PCI more frequently than after CB. In IHD patients with an EAT thickness of 8.5 to 10.2 mm measured with EchoCG in the atrioventricular groove, the risk of CEP was 4.3 times higher after myocardial revascularization than with thicker or thinner EAT regardless of the revascularization method.
Conclusion	An EAT thickness of 8.5 to 10.2 mm in the atrioventricular groove as measured with EchoCG was associated with a risk of adverse IHD course in patients who have underwent myocardial revascularization.

Keywords	Atherosclerosis; ischemic heart disease; epicardial adipose tissue; myocardial revascularization
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The past 10 years in the Russian Federation have seen an increase in the proportion of patients with coronary heart disease (CHD) [1], which now accounts for more than 40% of deaths in economically developed countries [2]. People with abdominal obesity, combined with hyperglycemia, dyslipidemia, and hypertension, are at higher risk of CHD [3]. However, existing models predicting the risk of cardiovascular disease (CVD) are not optimal [4]. The use of new cardiovascular risk markers will make it possible to more accurately determine the probability of CHD, severe course, and complications of the disease. Excessive epicardial adipose tissue (EAT) could be used as an independent risk factor [5].

EAT is a deposit of visceral fat that rests on the myocardium and is not separated by the fascia; it is located between the myocardium and visceral epicardium. EAT is supplied by the coronary arteries (CAs) [6]. Excessive EAT is deposited mainly along the coronary arteries (CAs), and adipokines and proinflammatory cytokines are secreted via paracrine and vasocrine mechanisms directly in the CAs, thus promoting the development of atherosclerosis [7–9]. Severe coronary atherosclerosis is associated with an increase in EAT volume [8–11]. Dozio et al. (2012) showed that in patients with CHD and severe coronary atherosclerosis after coronary artery bypass graft (CABG), EAT can be a potential source of proinflammatory interleukin-18 (IL-18) [12].

Park et al. (2016) identified the correlation between EAT thickness (echocardiography) and a higher rate of adverse clinical outcomes in patients with ST-elevation myocardial infarction (STEMI) after successful percutaneous coronary intervention (PCI). Their study is limited by the evaluation of EAT using ultrasound only at end-diastole; therefore the EAT thickness is underestimated [13]. No observational studies have analyzed the outcomes of various methods of myocardial revascularization, according to the thickness of EAT.

There are many cross-sectional studies of EAT's contribution to the development of subclinical and clinically significant coronary atherosclerosis [8, 11, 12]. There is, however, a need to perform prospective cohort studies to determine whether the volume of EAT can be used as an independent risk factor for cardiovascular complications (CVCs) in patients with CHD.

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Objective: To study the use of EAT in assessment of the risk for progression of CHD in patients after myocardial revascularization.

Materials and Methods

The study was approved by the ethics committee of First Pavlov State Medical University of St. Petersburg. All patients signed informed consent to participate in the study. The study complied with the principles of the Declaration of Helsinki.

It was a prospective cohort study to assess the predictive value of EAT thickness for adverse outcomes of CHD after PCI and CABG interventions. The follow-up period after myocardial revascularization varied from 1 to 54 months (mean of 41 months).

The study included 217 patients; 182 of them were diagnosed with clinically significant CHD, which required myocardial revascularization. PCI (angioplasty with stenting) was performed in 104 patients (median age 62 [57; 69] years). CABG was carried out in 78 patients (median age 66 [58; 69.5] years). Thirty-five patients with no CHD (median age 54 [51; 64] years) underwent cardiovascular examinations for other reasons unrelated to CHD.

The diagnosis of CHD was established by clinical manifestations, confirmed by stress tests and coronary angiography following the Russian Clinical Guidelines and the guidelines of the Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS) and developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI) [14–16].

The inclusion criterion for patients with CHD was the presence of a significant lesion in at least one CA, as characterized by more than 60% stenosis of the left coronary artery and more than 70% stenosis of other CAs. Patients with CHD had hemodynamically significant coronary stenosis shown by coronary angiography, which required the myocardial revascularization (angioplasty with stenting or CABG) [14–16].

Exclusion criteria were the following: familial hypercholesterolemia, secondary obesity, and hypertension, history of a stroke, chronic obstructive pulmonary disease, history of malignancy, chronic kidney disease, severe hepatic pathology, systemic connective tissue disease, acute rheumatic fever, infective endocarditis, hypothyroidism, hyperthyroidism, organic brain diseases, alcohol, and substance use disorders.

The volume of EAT was evaluated using two diagnostic imaging methods: echocardiography and cardiac computed tomography (CT).

Echocardiography was performed in all patients using an expert-class ultrasound scanner VIVID 7 Dimension (General Electric, USA). The main parameters were registered with a phased-array matrix sector probe M4S. The thickness of EAT was evaluated in millimeters by the mean value of three cardiac cycles with end-systole measurements at three points: above the apex, above the right ventricular (RV) free wall, and in the atrioventricular (AV) groove [17, 18].

Non-contrast-enhanced cardiac CT was executed on a CT scanner (Optima CT660). CT scanning was performed in the breath-hold mode in the area from the tracheal bifurcation to the diaphragm in the craniocaudal direction. The superior border of the heart marked the slice corresponding to the slice level of the pulmonary artery. The last slice of the myocardium or the last slice with a part of the descending artery was chosen as an anatomic landmark for the inferior border of the heart. The images were obtained using spiral CT scanning with retrospective ECG-gating. EAT is a compressible structure; therefore the images were reconstructed using the slices obtained at end-systole to avoid artificial reduction of fat thickness at diastole due to its compression of the myocardium [18, 19].

During analysis of the cardiac CT data, EAT was measured in millimeters at three locations: above the apex, above the RV free wall, and in the AV groove. The volume of epicardial fat was also estimated. The most valid parameter representing the amount of epicardial fat is the EAT volume measured during cardiac CT in cubic millimeters. We compared it with other CT and echocardiographic parameters characterizing the EAT. The CT assessment of epicardial fat was associated with high cost and limited indications for the examination; therefore only 76 examinations to measure EAT volume were executed using this method (41 and 35 exams in patients with and without CHD, respectively).

During the study, the rate of adverse outcomes after surgical treatment of CHD was evaluated. The outcome was a composite endpoint that included the following adverse events: death of unknown causes; fatal and nonfatal CVCs (death of CVD, acute coronary syndrome (ACS), nonfatal MI, transient ischemic attack); revascularization of any vascular territory (carotid endarterectomy, revascularization of the lower extremity arteries); repeat emergency myocardial revascularization (CABG or PCI); recurrence of angina symptoms; hospitalization for a worsening of chronic heart failure (CHF). If there were no outcomes of interest, the follow-up period ended on the day of the last contact with a patient.

Statistical analysis of data was performed using the SPSS software package, version 17.0 (SPSS Inc., USA).

The type of distribution of quantitative variables was verified by distribution histograms using the Shapiro-Wilk and Kolmogorov-Smirnov tests. As the distribution of most quantitative variables differed from normal, they were described using the median and quartiles, Me [Q_1; Q_3] [20]. The Z-test and the calculation of the z-criterion were applied for the analysis of data with a parametric distribution. Quantitative variables were compared using the Mann-Whitney and Kruskal-Wallis nonparametric tests [21]. Pearson's chi-squared test was used to compare qualitative variables [22]. The correlation between EAT and other parameters examined was identified using the Spearman's rank correlation coefficient (ρ) [23]. The influence of the factors were studied on the risk of coronary complications, and adverse outcomes were estimated using the method of analysis of event occurrence (time-to-event analysis, Kaplan-Meier analysis) and the multivariate Cox regression analysis, which made it possible to take into account the influence of factors on the outcome risk. The Kaplan-Meier survival function curves were compared using three tests: log rank, Breslow, and Tarone-Ware. During Cox regression analysis, the odds ratio (OR) of the outcome and its 95% confidence interval (CI) were calculated; the value of OR was used to quantify the effect of the factors studied on the outcome taking into account the follow-up time. The regression models were assessed using the coefficient of determination R2. Cox proportional hazards regression analysis was performed as a single- and multifactor analysis; all independent variables were included in the model by the forced input method [24, 25]. The differences were statistically significant if $p<0.05$.

Results

The age and sex of patients in the study are presented in Table 1.

The number of CHD patients with EAT volume measured by cardiac CT was limited, as routine chest CT to assess the volume of EAT is not carried out in this category of patients. We therefore searched for echocardiographic indices to be used as substitutes for CT indicators, which had a diagnostic value for EAT similar to that of EAT volume as measured by cardiac CT.

The analysis of the CT parameters of EAT in patients with CHD showed that the median volume of epicardial fat was 167.0 cm^3 [128.9; 207.1;], and 89.1 cm^3 [62.7; 102.7] in patients without CHD; $p<0.001$. Thus, according to CT, the EAT volume was significantly higher than in patients without CHD (see Table 2).

The presented data show that EAT volume as measured by CT is significantly correlated with patients' age, in subgroups of patients with and without CHD, as well as in the male and female subgroups (Table 2). Multiple linear regression analysis in patients with CHD showed that each subsequent year of life was associated with the increase of EAT volume by 1.4 cm^3 (95% CI, 1.0–1.9). No such trend was detected in subjects without CHD. The multifactor model was statistically significant and explained 74% of EAT variability (R2=0.743). Multiple linear regression analysis also revealed that the EAT volume in patients with CHD was higher by a mean of 56.7 cm^3 (95% CI, 46.6–66.8) than in patients without coronary pathology.

The EAT thickness measured in three different anatomical locations was compared between patients with CHD and subjects without CHD (Table. 3).

The thickness of EAT in patients with CHD was greater than that in subjects without coronary atherosclerosis, according to both cardiac CT ($p<0.01$) and echocardiography ($p<0.001$) in the AV groove. Significant differences were also identified in EAT thickness above the RV free wall, according to echocardiography ($p<0.05$), with a greater thickness in patients with CHD.

Table 1. Age and sex of patients with CHD and subjects without CHD

Parameter		Total sample (n=217)	Patients with CHD (n=182)	Patients without CHD (n=35)	Value	p
Age, years, Me [Q1; Q3]		58.5 [51.9; 66.0]	63.0 [57.0; 69.0]	54.0 [51.0; 64.0]	z=10.64	0.021
Sex, n (%)	Male	156 (71.8)	132 (72.5)	24 (68.6)	χ^2=71.367	<0.001
	Female	61 (28.2)	50 (27.5)	11 (31.4)		

Table 2. Results of correlation analysis of the epicardial adipose tissue volume as estimated by cardiac CT and age of patients

Parameter		n	ρ	p
Regardless of sex and the presence of CHD		76	0.482	< 0.001
According to sex	Male	52	0.376	0.006
	Female	24	0.579	0.003
According to the presence of CHD	Patients with CHD	41	0.697	< 0.001
		35	0.340	0.046

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Measured using echocardiography, the thickness of EAT in all three locations was significantly less than according to CT regardless of the presence or absence of CHD.

Correlation analysis revealed the strongest relationship between the volume of EAT according to CT and the thickness of EAT in the AV groove, according to echocardiography (ρ=0.631; p<0.001). The relationship between EAT volume according to CT and EAT thickness according to echocardiography was also significant but less strong above the RV free wall (ρ=0.602; p=0.008), and least strong for EAT thickness above the apex according to echocardiography (ρ=0.332; p<0.042).

Thus the thickness of EAT in the AV groove may be considered to be most strongly correlated with EAT volume as measure by cardiac CT. Accordingly, this parameter is considered to be the most consistent with the volume of EAT (by cardiac CT). The EAT thickness over the AV groove, as measured by echocardiography, was used in the subsequent analysis of data.

The rate of adverse outcomes after the surgical treatment of CHD is shown in Table 4.

Clinical, angiographic, and echocardiographic characteristics of patients with CHD, according to the method of myocardial revascularization at the time of inclusion, are shown in Table 5.

The subgroups of patients with CHD who underwent CABG and PCI with stenting were comparable in the main clinical laboratory and instrumental test results. However, patients in the CABG group more often presented with CHF FC III and IV and less often received ACE inhibitors and statins; they also had higher levels of total cholesterol than patients in the PCI group. CT showed that the rate of single-vessel disease was higher in the PCI group.

After myocardial revascularization using one of two methods, the follow-up period in the prospective study was from 1 to 54 months, with a mean of 41 months. EAT thickness in the AV groove and the rate of onset of the composite endpoint are shown in Table 6.

In the group of patients with CHD, the proportion of those with reported onset of composite endpoint was significantly correlated with the method of myocardial revascularization and was higher in patients who underwent PCI with stenting. To assess the prognostic role of EAT volume in relation to adverse outcomes after surgical

Table 3. Thickness of the epicardial adipose tissue layer as estimated by cardiac CT and echocardiography in the study groups

Presence of CHD	Thickness of EAT	Method of measurement	Me [Q1; Q3]	z	p
Patients with CHD (n=41)	Above the apex	CT	6.0 [5.0; 7.0]	-4.553	< 0.001
		Echocardiography	2.9 [2.0; 3.6]		
	Above RV	CT	6.0 [5.0; 7.0]	-2.511	0.01
		Echocardiography	4.9 [3.8; 6.5]		
	Above the AV groove	CT	12.0 [9.0; 15.0]	-4.586	< 0.001
		Echocardiography	7.6 [5.5; 9.7]		
Patients without CHD (n=35)	Above the apex	CT	6.3 [5.0; 7.0]	-3.850	< 0.001
		Echocardiography	2.0 [1.5; 2.9]		
	Above RV	CT	6.0 [5.0; 6.5]	-3.605	< 0.001
		Echocardiography	2.6 [1.9; 3.0]		
	Above the AV groove	CT	9.5 [7.3; 13.4]	-3.473	0.001
		Echocardiography	3.5 [2.1; 4.0]		

Me [Q_1; Q_3], median and inter-quartile range; CHD, coronary heart disease;
EAT, epicardial adipose tissue; CT computed tomography; RV, right ventricle; AV, atrioventricular.

Table 4. Structure of composite endpoint

Endpoint, n (%)	Total (n=53)	CABG (n=13)	PCI (n=40)
Deaths of unknown causes	2 (3.7)	2 (15.3)	0 (0.0)
Deaths of CVDs	7 (13.2)	6 (46.2)	1 (2.5)
Nonfatal MI	3 (5.7)	0	3 (7.5)
ACS	8 (15.1)	1 (7.7)	7 (17.5)
Recurrence of the angina symptoms	19 (35.8)	1 (7.7)	18 (45)
Hospitalization for a worsening of CHF	3 (5.7)	0	3 (7.5)
Nonfatal stroke	1 (1.9)	0	1 (2.5)
Repeat emergency myocardial revascularization	10 (18.9)	3 (23.1)	7 (17.5)

CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention;
CVDs, cardiovascular diseases; MI, myocardial infarction; ACS, acute coronary syndrome; CHF, chronic heart failure.

Table 5. Baseline clinical, angiographic, and echocardiographic data of patients according to treatment of CHD

Parameter		Total number of patients with CHD (n=182)		Method of treatment	Value	p
		CABG (n=78)	PCI (n=104)			
Sex, n (%)	Male	132 (72.5)	59 (75.6)	73 (70.2)	χ^2=0.797	0.372
	Female	50 (27.5)	19 (24.4)	31 (29.8)	χ^2=0.651	0.163
Age, years; Me [Q1; Q3]		63.0 [57.0; 69.0]	66.0 [58.0; 69.5]	62.0 [57.0; 69.0]	z=–0.550	0.582
Family history of CVDs, n (%)		58 (33.1)	19 (24.4)	39 (37.3)	χ^2=3.978	0.056
Essential hypertension, n (%)		166 (91.5)	71 (91.0)	95 (91.7)	χ^2=0.032	0.857
CHF						
FC I, n (%)		13 (7.2)	4 (5.1)	9 (8.7)	χ^2=1.958	0.096
FC II, n (%)		132 (71.9)	60 (76.9)	72 (69.4)	χ^2=3.758	0.059
FC III, n (%)		21 (10.6)	12 (16.7)	9 (8.7)	χ^2=14.256	0.007
FC IV, n (%)		2 (1.4)	0 (0.0)	2 (1.9)	χ^2=10.256	0.001
DM type 2, n (%)		43 (23.0)	20 (25.6)	23 (21.7)	χ^2=0.468	0.494
Smoking status at the time of inclusion, n (%)		89 (49.4)	37 (47.4)	52 (50.3)	χ^2=0.173	0.677
Beta-blockers, n (%)		169 (91.1)	76 (95.9)	93 (88.7)	χ^2=3.093	0.079
ACE inhibitors, n (%)		93 (51.2)	33 (41.7)	60 (57.8)	χ^2=11.469	0.001
Sartans, n (%)		41 (22.5)	13 (16.4)	28 (27.4)	χ^2=3.228	0.072
Calcium channel blockers, n (%)		55 (30.9)	22 (28.2)	33 (32.2)	χ^2=0.362	0.547
Statins, n (%)		160 (87.9)	59 (75.3)	101 (96.7)	χ^2=24.734	< 0.001
Antiplatelet drugs						
None, n (%)		18 (9.9)	13 (16.9)	5 (4.8)	χ^2=8.217	0.032
Acetylsalicylic acid, n (%)		105 (57.7)	51 (65.7)	54 (52.0)	χ^2=4.072	0.069
Clopidogrel, n (%)		46 (25.3)	10 (13.3)	36 (34.6)	χ^2=8.195	0.009
Ticagrelor, n (%)		12 (6.5)	3 (4.1)	9 (8.7)	χ^2=7.044	0.058
Coronary angiography: number of affected arteries						
1, n (%)		41 (22.5)	8 (10.3)	33 (32.2)	χ^2=15.560	< 0.001
2, n (%)		46 (25.1)	19 (24.4)	27 (25.5)	χ^2=0.668	0.794
3, n (%)		45 (23.8)	23 (29.5)	22 (21.2)	χ^2=0.181	0.194
4 and more, n (%)		48 (26.4)	28 (35.9)	22 (21.2)	χ^2=8.261	0.004
Echocardiography						
Regions of wall motion abnormality						
• Hypokinesia		27 (14.8)	9 (12.1)	18 (17.0)	χ^2=4.334	0.195
• Akinesia		31 (17.0)	12 (15.1)	19 (18.1)	χ^2=1.740	0.356
• Hypo- and akinesia		26 (14.2)	12 (15.1)	14 (13.2)	χ^2=3.704	0.215
LVEF, %, Me [Q1; Q3]		65.0 [60.0; 68.0]	61.0 [58.0; 65.3]	59.0 [45.0; 67.0]	z=–2.476	0.129
Objective data						
SBP, mmHg; Me [Q1; Q3]		130 [120; 145]	130 [120; 140]	130 [120; 145]	z=–0.522	0.602
DBP, mmHg; Me [Q1; Q3]		80 [78; 90]	80 [80; 85]	80 [70; 90]	z=–1.473	0.141
Pulse, bpm, Me [Q1; Q3]		71 [64; 78]	70 [61; 77]	66 [60; 74]	z=–1.397	0.163
WC [Q1; Q3]		99.0 [91.7; 109.0]	96.5 [91.0; 105.0]	98.0 [92.0; 108.0]	z=–2.710	0.227
BMI, kg/m^2; Me [Q1; Q3]		30.5 [27.2; 33.9]	27.8 [25.8; 31.3]	28.4 [25.7; 32.0]	z=–0.783	0.434
Biochemical blood analysis						
Total cholesterol, mmol/L, Me [Q1; Q3]		5.24 [4.45; 6.10]	4.69 [3.89; 5.73]	4.30 [3.77; 4.90]	z=–2.343	0.019
LDL cholesterol, mmol/L, Me [Q1; Q3]		3.25 [2.41; 4.27]	2.29 [1.66; 3.34]	2.30 [1.84; 3.03]	z=–1.120	0.263
HDL cholesterol, mmol/L, Me [Q1; Q3]		1.22 [1.02; 1.47]	1.23 [1.13; 1.49]	1.23 [1.12; 1.47]	z=–1.327	0.185
Triglycerides, mmol/L, Me [Q1; Q3]		1.60 [1.20; 2.21]	1.43 [1.06; 2.19]	1.60 [1.32; 2.14]	z=–0.359	0.719
Glucose, mmol/L, Me [Q1; Q3]		5.5 [5.1; 6.0]	5.6 [5.2; 6.5]	5.8 [5.4; 6.8]	z=–2.429	0.065
C-reactive protein, mg/L, Me [Q1; Q3]		3.24 [2.51; 4.64]	3.0 [2.11; 4.23]	3.2 [2.41; 4.63]	z=–1.945	0.341

n, number of examinations; z, parametric variable test; χ^2, Pearson's chi-squared test; CHD, coronary heart disease; CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention; CVD, cardiovascular disease; CHF, chronic heart failure; FC, functional class; DM, diabetes mellitus; ACE, angiotensin-converting enzyme; SBP, systolic blood pressure; DBP, diastolic blood pressure; WC, waist circumference; BMI, body mass index; LVEF, left ventricular ejection fraction: LDL, low-density lipoproteins; HDL, high-density lipoproteins.

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Table 6. Thickness of EAT and rate of onset of CVDs

Parameter	CABG (n=78)	PCI (n=104)	Value	p
EAT thickness in AV groove, echocardiography, mm, Me [Q1; Q3]	8.4 [5.7; 9.7]	8.5 [5.9; 10.3]	z=-1.121	0.262
Onset of the composite endpoint, n [%]	13 [16.7]	40 [38.5]	$\chi 2$=10.258	0.001

n, number of examinations; z, parametric variable test; $\chi 2$, Pearson's chi-squared test;
PCI, percutaneous coronary intervention; EAT, epicardial adipose tissue; AV, atrioventricular.

treatment of CHD, the EAT thickness in the AV groove, as measured by echocardiography, was found to be the most strongly correlated with the volume of EAT according to cardiac CT.

To identify prognostically significant gradations of this parameter of EAT, it was ranked by quartiles (only values of patients with CHD were included in the calculation):

- Less than Q_1:<5.79 mm
- Q_1 – Q_2: 5.79–8.45 mm
- Q_2 – Q_3: 8.46–10.20 mm
- More than Q_3>10.20 mm

A preliminary analysis of onset of the composite endpoint was made using the Kaplan-Meier test with quartile ranking of EAT thickness in the AV groove according to echocardiography.

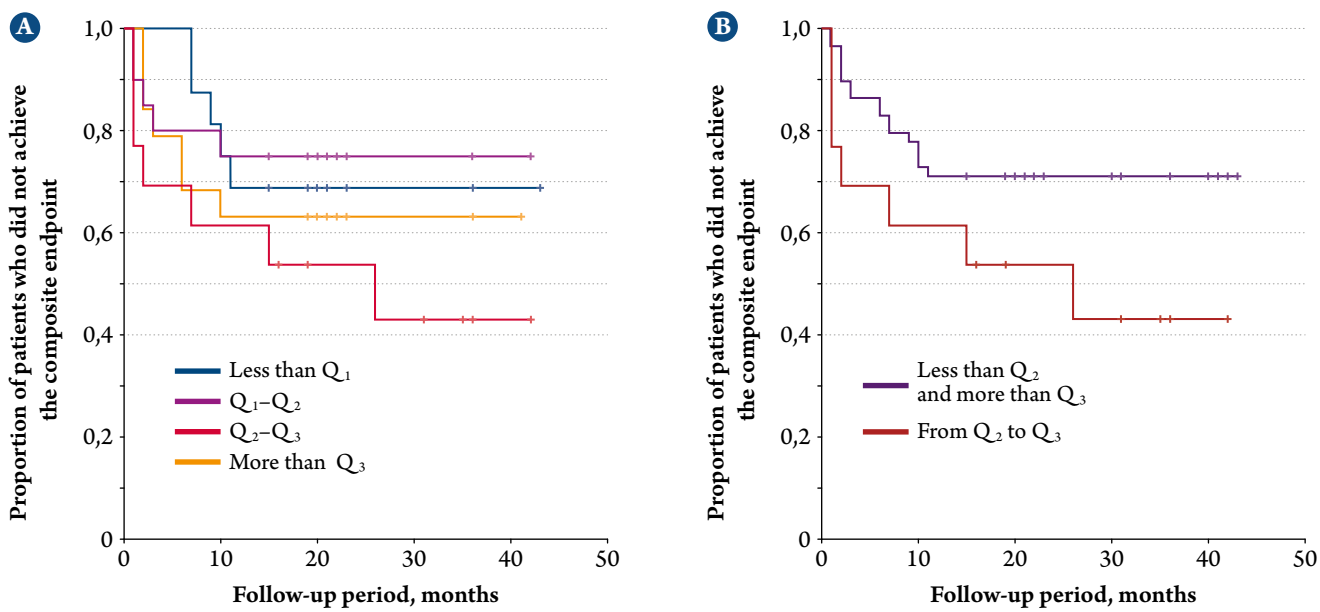
The time-to-composite endpoint curve in CHD patients with the amount of EAT corresponding to the 2nd to 3rd quartile values is located significantly lower than the curves in patients with other values of EAT thickness – that is, it shows the adverse outcome of the disease after myocardial revascularization in this subgroup of patients (Figure 1A). Therefore, further data analysis in all patients with CHD, values of EAT thickness below the 2nd quartile, and above the 3rd quartile were combined with an independent allocation of gradation from the 2nd to 3rd quartile (Figure 1B).

The results of comparison of the Kaplan-Meier time-to-composite endpoint curves for different gradations of the EAT parameter are given in Table 7.

Separation of the EAT parameter of interest into two gradations, including the allocation of gradation from the 2nd to 3rd quartile, resulted in identifying that the differences between the time-to-composite endpoint curves were close to statistical significance, which suggests an adverse prognostic role of this volume of EAT, which can be considered «above the mean,» but far below the maximum possible values in this group of patients with CHD.

To verify this hypothesis, a multivariate Cox regression analysis was carried out using composite endpoint as a dependent variable, and the value of the EAT parameter from the 2nd to 3rd quartile as a predictor variable in this population of patients with CHD. The multifactorial analysis revealed the prognostic value of an EAT thickness

Figure 1. The Kaplan-Meier curves are used to present time to onset of the composite endpoint according the ranking of thickness of the epicardial adipose tissue in the atrioventricular groove (as measured by echocardiography) by the quartiles (A) and two quartile gradings (B)



from 8.5 to 10.2 mm in the AV groove as measured by echocardiography as a predictor of adverse outcome of CHD after PCI and CABG interventions. Thus, with an EAT thickness from 8.5 to 10.2 mm, the risk of onset of composite endpoint increased 4.3 times (95% CI, 1.2–15.3; p=0.023) as compared with measurements of EAT thickness below and above these limits.

Discussion

The volume of EAT is known to correlate with the amount of intra-abdominal fat and risk factors for the development of CVCs, such as hypertension, atherogenic dyslipidemia, insulin resistance, hyperleptinemia, and increased C-reactive protein and fibrinogen [5, 6, 8, 10, 15]. Results of earlier studies showed that the amount of EAT in patients with CHD and metabolic syndrome also increases with age. Possible reasons for the increase in visceral fat with aging include reduced synthesis of sex steroid hormones, changes in cortisol production, decreased levels of endocannabinoids, insulin hyposensitivity of peripheral tissues, and reduced physical activity [12, 26]. We determined that the volume of EAT increases with every year in patients with CHD by 1.4 cm^3. These findings are consistent with the results of a cardiac autopsy investigation showing the relationship between an increase in the amount of EAT and patients' age irrespective of the cause of death [27].

During the real-world clinical examination of patients, the actual amount of EAT is presented as its volume as measured by highly sensitive imaging methods of examination (CT or magnetic resonance imaging) [7]. However, these precise diagnostic methods are expensive and cannot be used in everyday clinical practice to assess epicardial obesity. According to our findings, among the indicators of EAT evaluated by echocardiography, its thickness as measured in the AV groove correlated most strongly with the volume of EAT according to cardiac CT; therefore, we used the former in the analysis of data. The decreasing strength of the correlation between the thickness and volume of EAT has been observed when measurements move from the base to the apex of the heart. Our findings are consistent with previous work showing the greatest thickness of EAT at the base of the heart, decreasing toward the apex [27].

Table 7. Results of comparison of Kaplan-Meier curves of time-to-onset of the composite endpoint for different gradations of epicardial adipose tissue

Number of curves being compared	Comparison test	χ^2	p
4 gradations	Log rank	3.533	0.316
	Breslow	3.115	0.374
	Tarone-Ware	3.211	0.360
2 gradations	Log rank	3.057	0.050
	Breslow	2.703	0.100
	Tarone-Ware	2.776	0.096

The proatherogenic effect of EAT described in the literature is associated with the development of subclinical carotid atherosclerosis [28]. It is likely to result in an increased risk of the development and progression of CHD [19, 29]. Therefore, assessment of the role of EAT is very clinically significant in the pathogenesis of clinical manifestations and complications of CHD, including sudden cardiac death, ACS, relapse of clinical manifestations of exertional angina or increase in the functional class of exertional angina after myocardial revascularization, development of CHF, shunt thrombosis, stent thrombosis, stent restenosis, and stroke [18, 20, 29, 30].

Our findings show that the onset of CVCs (i.e., composite endpoint) was more common in patients who underwent PCI with coronary stenting than in patients who underwent CABG, which is consistent with the literature [31, 32]. The structure of the composite endpoint was represented mainly by the relapse of angina symptoms (more frequently in the PCI group), the need for acute rerevascularization (more frequently in the PCI group). The least common complications were cases of death of unknown causes (only in the CABG group), nonfatal MI, stroke, and hospitalization due to the deterioration of CHF (reported only in patients after PCI with coronary stenting).

The one-way regression analysis revealed that, in patients with CHD after PCI with coronary stenting, the risk of onset of the composite endpoint is 3.38 times higher than after CABG. This finding is consistent with the data of meta-analyses and individual studies on the greater frequency of recurrences of angina and rerevascularizations after PCI as compared with CABG in the case of isolated lesions of the left anterior descending (LAD) artery [33, 34]. However, there were no statistically significant differences in mortality, the rate of MI, or the rate of stroke between the two methods of revascularization in the case of isolated lesions of the LAD artery [35]. The randomized clinical studies, which included 6,055 patients with multivessel coronary artery disease (3,023 cases of CABG and 3,032 cases of PCI) and compared long-term complications after CABG (arterial shunts) and PCI, demonstrated significantly lower mortality, rate of recurrent MI, and rate of re-revascularization in patients who underwent CABG, irrespective of diabetes status [36]. It should be noted that in severe multivessel coronary artery disease, CABG

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was accompanied by a lower total death rate and mortality from CVDs, a lower rate of recurrent MI, and a lower rate of myocardial re-revascularizations than PCI [37].

The multiway analysis performed in this study revealed that with a thickness of EAT from 8.5 to 10.2 mm measured by echocardiography in patients with CHD in the AV groove, the risk of onset of the composite endpoint was on average 4.3 times higher than with lesser or greater thickness of EAT.

These data are consistent with earlier findings on the relationship of epicardial obesity and the development of coronary atherosclerosis [38], and with the results of the examination of patients with ACS and EAT thickness of 7.5 mm who developed fatal and nonfatal MI and strokes more often (than patients without CHD and with the mean EAT thickness of 5 mm). This work was limited by the fact that the EAT thickness was assessed only by 2D echocardiography and only above the RV free wall at end-diastole [39].

In our prospective observation, the EAT thickness of 10.2 mm in patients with CHD after myocardial revascularization was more rarely associated with adverse cardiovascular complications. This phenomenon cannot be explained definitively: despite the potentially negative role of abdominal obesity, the recent epidemiological data show that the life expectancy of subjects with CVDs and overweight/class I obesity was higher than in patients with normal body mass index (BMI) [40]. Similar data were described by Hastie et al. in their prospective clinical study [41]. In the literature, this is conventionally called the «obesity paradox» [40, 41] The clinical and pathogenetic basis of this phenomenon should be investigated further.

At the same time, the measure of EAT thickness that is clearly associated with a high risk of CVCs was not found. Some authors state that the signs of subclinical atherosclerosis manifest with a thickness of 7 mm. According to other authors, insulin resistance and increased risk of acute cardiovascular events are highly probable if the thickness of EAT is greater than 9 mm [5, 6, 8, 28].

Based on these findings, high cardiovascular risk cannot be determined only by the known factors. Attention should be given to the thickness of EAT, which perhaps is of greater prognostic significance than the measures of BMI and waist circumference [42]. It was shown that epicardial obesity in people with normal BMI and waist circumference might indicate a higher risk of the development of CHD and the need for preventive measures [43].

Further pivotal and clinical studies are therefore necessary to clarify the role of EAT in the pathogenesis of coronary atherosclerosis and the development of its complications, as well as to develop the treatment approaches for such patients.

Conclusion

1. The volume and thickness of the epicardial adipose tissue in patients with coronary heart disease are greater than in subjects without coronary atherosclerosis.
2. Prospective monitoring of patients with coronary heart disease showed that cardiovascular complications in patients after percutaneous intervention for coronary stenting were more common than in those who underwent coronary artery bypass grafting.
3. Patients with coronary heart disease with an epicardial adipose tissue layer from 8.5 mm to 10.2 mm, as measured by echocardiography in the atrioventricular groove, were at 4.3 times higher risk of onset of a composite endpoint after myocardial revascularization than such patients with a greater or lesser thickness of the epicardial fat layer regardless of type of coronary intervention.

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