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ORIGINAL ARTICLES

Relationship between the degree of epicardial fat volume and severity of coronary atherosclerosis

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Summary

Background

Obesity is associated with high level of cardiovascular morbidity and mortality. During the last years it has been clarified that high cardiovascular risk correlates not only with total volume of adipose tissue, but mostly with increased amount of visceral fat tissue. Epicardial fat tissue is the most studied local visceral fat depot and a potent source of pro-inflammatory, pro-atherogenic, and neurohumoral factors.

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Objective

To investigate the relationship between the degree of epicardial fat volume and coronary atherosclerosis severity

Materials and methods

This study included 156 men with coronary heart disease (CHD) aged 53.2±7.6 years with obesity I–III grade, BMI 34.5±5.6 kg/m^2. All patients underwent measurement of metabolic and additional cardiovascular risk factors and coronary angiography. Epicardial fat tissue thickness (EFT) was evaluated using transthoracic echocardiography.

Results

The highest values of EFT were observed in the group of patients with multiple stenosis of coronary arteries where EFT reached 10 (8; 10) mm. ROC-analysis revealed EFT as a predictor of significant coronary atherosclerosis in patients with CHD. Sensitivity and specificity of this marker were 80.4 % and 67.6 %, respectively (cut-off value=6 mm). It was found that EFT correlated significantly with the presence and severity of coronary atherosclerosis together with age, leptin and resistin levels, and waist circumference.

Conclusions

Our results prove the necessity of addition of obesity-correcting measures, targeting first of all visceral obesity, into programs of atherosclerosis prevention including coronary atherosclerosis.

Key words

Epicardial fat tissue, coronary atherosclerosis

Obesity has become one of the major health problems in the world because it is associated with a high level of cardiovascular morbidity [1]. The prevalence of obesity in the world has grown more than twice during the period from 1980 till 2014 [2]. According to the ESSE study, the obesity takes the third place among cardiovascular risk factors after dyslipidemia and hypertension [3]. Obesity is also regarded as a risk factor for the high level of mortality among general population. The lowest level of mortality is shown when the BMI is in the range of 20–24 kg/m^2 (non-smokers in American and Russian populations) and starts getting higher if the BMI is below or above that range [4].

During the last years it has become clear that the high cardiovascular risk is associated not only with the total adipose tissue volume, but especially with the increase of visceral adipose tissue (VAT) amount which is concentrated in local fat depots. The best-studied local fat depot of visceral adipose tissue is EAT which lies between visceral pericardium and myocardium [5]. Due to the close anatomical and functional relationships with the myocardium, EAT has a direct impact on the coronary vessels morphology through paracrine mechanisms [6, 7]. There is no anatomical barrier between the EAT layer and the myocardium, but there are common systems of blood supply (coronary vessels) and of microcirculation. Many neurohumoral factors produced by VAT and in particular by EAT, such as, adipokines, cytokines, proteins which control lipid metabolism, have a potent pro-atherogenic effect and can stimulate the development of coronary artery atherosclerosis [8, 9].

The **objective of the research** is to study the relationship between the grade of epicardial obesity and the severity of coronary atherosclerosis.

Materials and methods: the study was conducted in Altai regional cardiologic clinic in the period from 2011 till 2016. The study's protocol was approved by the ethics committee. The study included 156 men with ischemic heart disease (IHD) in the age of 53.2±7.6 and with the obesity of I–III grades. All patients underwent coronary angiography. Patients with diabetes mellitus type 2 and those who had undergone the acute myocardial infarction were excluded from the study.

The laboratory exams were held: total cholesterol (TC), serum triglycerides (TG) measured by the enzymatic method using test kits; high density lipoprotein cholesterol (HDL cholesterol) in supernatant plasma. The cholesterol of low-density lipoproteins (LDL cholesterol) was calculated using the Frivald formula. The glucose content in capillary blood was determined by the glucose oxidase method. The serum leptin and resistin levels were determined by enzyme immunoassay (BioSource sets, Belgium). The determination of the main apolipoproteins — apolipoprotein A1 (ApoA1) and apolipoprotein B (ApoB) — was carried out by immunoprecipitation method using a Konelab analyzer.

Anthropometric measurements were performed to estimate total obesity by body mass index (BMI) and abdominal obesity by waist circumference (WC). Epicardial obesity was assessed by transthoracic echocardiography in B-mode on a Vivid 5 device with a 3.5 MHz mechanical sector sensor. Three cardiac cycles were registrated in parasternal positions on the long and short axes of the left ventricle [10]. The maximum thickness of epicardial fat was visualized behind the free wall of the right ventricle when the measurement was performed along the perpendicular to the aortic ring, which was used as an anatomical landmark. All patients underwent diagnostic CAG using the Philips Integris 3000 device (USA).

Statistical data processing was performed using the program STATISTICA 6.1., MedCalc 5.4. For each of the continuous values of normal distribution, the mean (M) and standard deviation (SD) are given; for the quantities with abnormal distribution, the median (Med) and the upper and lower quartiles (UQ; LQ) are shown. The normal distribution hypothesis was tested using the Shapiro-Wilk criterion. The hypothesis of mean tEAT values equality in different groups was tested using the Kruskal-Wallis method. The statistical description of the relationship between the various parameters was carried out by calculating the Spearman's rank correlation coefficient. A ROC-curve was constructed to estimate the sensitivity and specificity of tEAT as a prognostic criterion. The univariate binary logistic regression method was used to evaluate the effect of various predictors on the development of hemodynamically significant coronary atherosclerosis. The level of statistical significance was $p < 0.05$.

Results and discussion: we performed the evaluation of the relationship between the EAT thickness (tEAT) and main and additional metabolic risk factors (RF), the age and BMI using correlation analysis. We have found out that tEAT correlates significantly with plasma lipids: TG ($r = 0.396$; $p < 0.001$), HDL ($r = -0.295$; $p = 0.004$), ApoA ($r = -0.317$; $p = 0.002$), and ApoB ($r = 0.357$, $p < 0.001$), In addition, a positive relationship was showed between the tEAT value and some proatherogenic neurohumoral factors of visceral fat such as leptin ($r = 0.592$; $p < 0.001$) and resistin ($r = 0.247$; $p = 0.023$) (Figure 1).

No significant relationship was showed between tEAT and the level of systolic and diastolic blood pressure (SBP and DBP), as well as the glucose level, which can possibly be explained by the fact that most patients with arterial hypertension were getting an adequate antihypertensive therapy and patients with impaired carbohydrate metabolism were not included in the study. We also found no relationship between tEAT and BMI ($r=0.135$; $p=0.114$). It can be explained by the fact that BMI reflects the total obesity degree

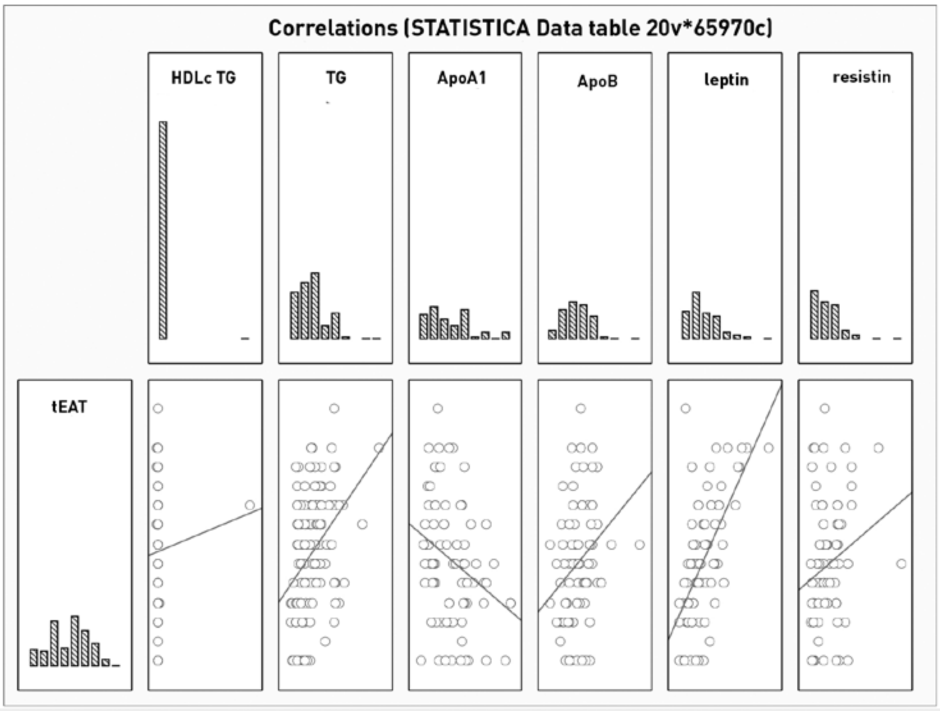

Figure 1. The relationship between tEAT and metabolic risk factors (Spearman correlation analysis)
(HDLc — high density lipoprotein cholesterol, TG — triglycerides, ApoA1 — apoprotein A1, ApoB — apoprotein B, tEAT — thickness of epicardial adipous tissue)

when a significant part of adipose tissue is represented by the inert subcutaneous fat which does not produce adipokines and other proatherogenic neurohumoral factors, in contrast to the neurohumorally active visceral adipose tissue. That's why, possibly, the BMI obesity was not shown to be associated with the cardiovascular risk increase in most studies [10.11]. But visceral adipose tissue, including epicardial adipose tissue, is a source of pro-inflammatory and prothrombotic cytokines, such as, tumor necrosis factor (TNFα), monocyte chemoattractant protein (MCP-1), interleukins 1 and 6 (IL-1, IL-6), resistin, omentin, leptin, visfatin, inhibitor of tissue plasminogen activator (PAI-1) and angiotensinogen [12.13]. Thus, the hormonal activity of epicardial adipose tissue was studied in 42 patients who underwent coronary artery bypass grafting surgery, and it was found that EAT produces proinflammatory cytokines IL-1, IL-6 and TNFα, as well as chemokine MCP-1, having a potent effect on the bloodstream [14]. It was also found that the EAT thickness increase of more than 7 mm in women was associated with subclinical coronary arteries atherosclerosis [15]. In another study (n = 998), it was proved that the EAT volume increase, assessed by computed tomography, was associated with a high risk of coronary heart disease development during 5 years of observation, regardless of gender [18].

After that we performed the analysis of the relationship between the degree of epicardial obesity and the prevalence and the severity of coronary vessel impairment. According to the results of the performed CAG, several groups of patients were identified on the grounds of the quantity of impaired arteries. The first group included patients with single-vessel coronary lesion (n=27), the second — two-vessel lesion (n=54), the third — three-vessel lesion (n=54), and the fourth group consisted of patients with multiple coronary stenosis and the diffuse impairement of coronary vessels (n=18). Analyzing the mean values of tEAT, it was found that the highest mean tEAT values were in the group of patients with multiple coronary stenosis and were 10 (8;10) mm, the lowest mean tEAT values were in patients with single-vessel and two-vessel lesions and were 3 (2;5) mm and 4 (2;8) mm respectively. Thus, the difference between the groups was statistically significant (p=0.004) (figure 2).

Figure 3 and 4 show a coronary angiogram and an echocardiogram of a patient with multiple coronary stenosis and significant epicardial obesity with the tEAT of 13 mm.

Taking in consideration the found relationship between tEAT and coronary vessels impairment in patients with obesity, we performed the evaluation of tEAT informativity in detecting hemodinamically significant stenosis of CA (>70 %) using ROC-analysis (figure 5).

As a criterion for diagnostic effectiveness, the area under the ROC curve (AUC) was measured (figure 5). It was 0.740 and this indicates a good classification quality of tEAT (p=0001). The obtained AUC value differs significantly from the area above the diagonal (0.5) with p = 0.0001. The sensitivity of the ROC model

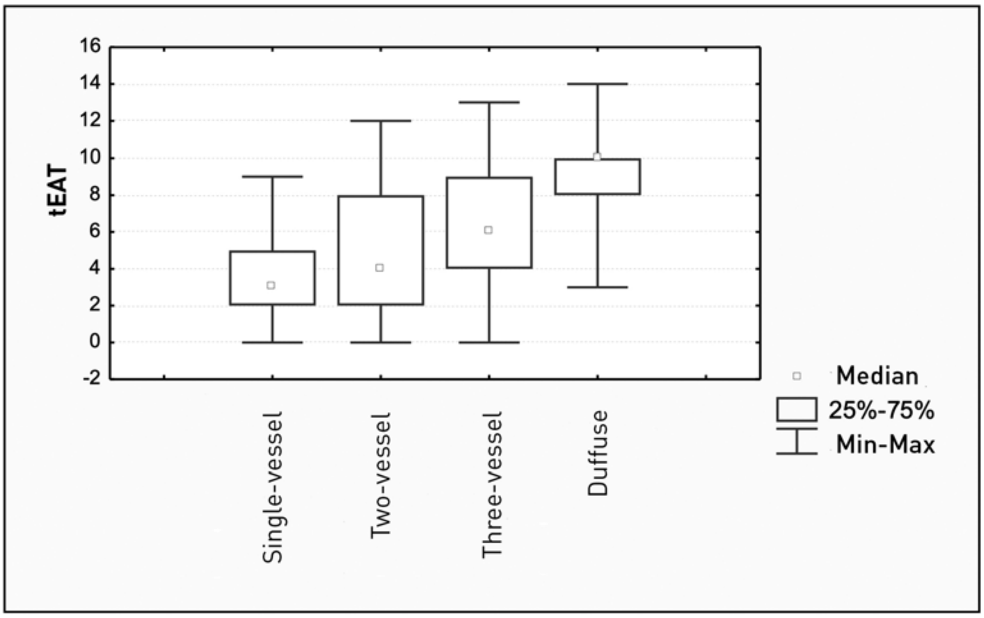

Figure 2. tEAT values in patients with different degrees of coronary vessels impairment

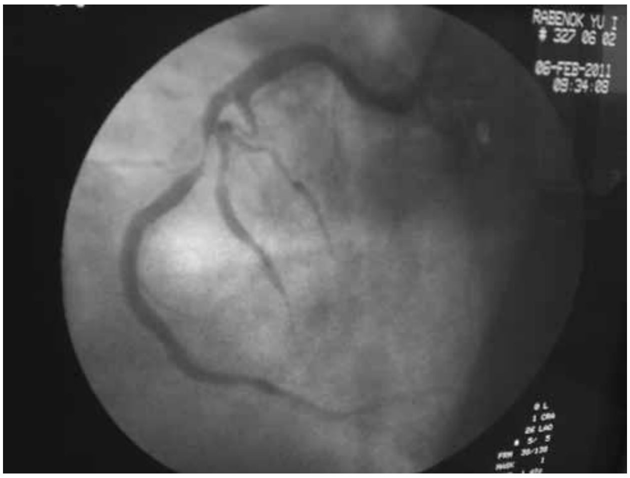

Figure 3. Coronary angiogram of N patient

Figure 4. Echocardiogram of N patient. EAT is indicated by the arrow.
Note: Area under the ROC curve (AUC) — 0.740; Standard error –0.0437; 95 % Confidence interval 0.653 to 0.814; z statistic –5.487 Significance level P (Area=0.5) – 0.0001

(the fraction of truly positive classification results which is the presence of a severe stenosis) is 80.4 %, the specificity (the fraction of truly negative classification results which is the absence of any significant stenosis) is 67.6 %. The cut-off value for tEAT was found to be 6 mm. Thus, a tEAT ⩾ 6mm is a predictor of significant coronary atherosclerosis in patients with CHD.

The obtained data are confirmed by another study conducted in Corea (n=557) which showed that the tEAT increase of more than 3 mm was an independent risk factor of coronary atherosclerosis with more than 50 % stenosis presence [16].

After that we studied the influence of different predictors on the development of severe coronary atherosclerosis, using univariate binary logistic analysis. In addition to tEAT, there were age and main metabolic risk factors among the predictors: WC, TG, HDL cholesterol, glucose, systolic and diastolic blood pressure (SBP, DBP), and some additional cardiovascular risk factors, such as ApoA1, ApoB, leptin and resistin.

Table 1. **Results of univariate binary logistic analysis of coronary atherosclerosis predictors**

Predictors	OR	95 %CI	χ^2	p
Age	6.52	2.61–15.9	10.06	<0.001
tEAT	4.41	2.02–9.43	22.31	<0.001
Leptin	3.50	1.46–8.37	11.65	<0.001
Resistin	3.13	1.32–7.42	10.89	<0.001
WC	1.72	0.76–3.74	5.63	<0.01

Note: OR — odds ratio; CI — confidence interval; WC — waist circumference; tEAT — epicardial adipose tissue thickness

The performed analysis showed that tEAT, together with age, resulted in being the significant predictor of coronary atherosclerosis in patients included in the study (table 1). Moreover, the similar relationship was demonstrated with leptin, resistin and WC levels.

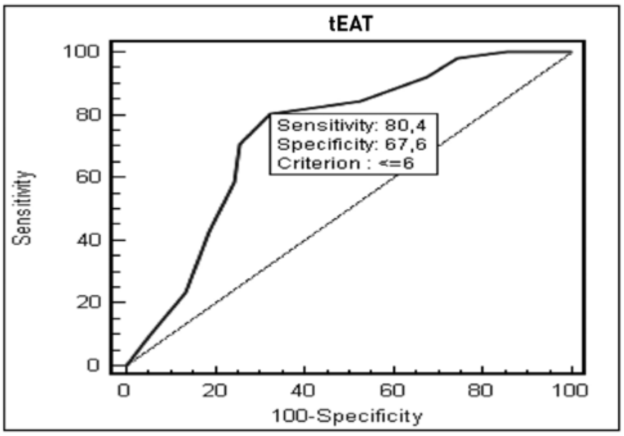

Figure 5. ROC-curve for estimating the informativity of tEAT as the stenosing coronary atherosclerosis predictor (tEAT — epicardial adipose tissue thickness).

It is important that when comparing epicardial and abdominal obesity (using the WC value) as coronary atherosclerosis predictors, the tEAT resulted in being more significant (OR 4.44; 95 % CI 2.06–9.59; p<0.001) than WC (OR 1.65; 95 %CI 0.72–3.80; p=0.018). The lipid metabolism markers (TG, HDL cholesterol, ApoA1, ApoB), SBP and DBP levels were not informative as predictors, probably because patients were getting an adequate hypolipidemic and hypotensive therapy in the course of 1–6 months.

Thus, our study found out the relationship of tEAT with plasma level (HDL cholesterol, TG), apolipoproteins (ApoA1, ApoB), visceral fat hormones (leptin, resistin). It was also found that patients with severe coronary impairment had higher average tEAT values. It was also showed that according to ROC-curve the tEAT ⩾ 6 mm in patients with obesity and CHD was informative for diagnostics of stenosing coronary atherosclerosis, which was proved by univariate binary logistic analysis. The gotten results demonstrate the necessity of obesity correction measures, especially those regarding visceral obesity, in atherosclerosis (including coronary atherosclerosis) prevention programs.

Conflict of interest: None declared

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