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Epicardial Fat as a Risk Factor for Cardiovascular Disease

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Abstract: Epicardial fat is one of the most discussed and unexplored risk factor for cardiovascular disease. Structure of epicardial adipose tissue, it's functions and pathophysiological processes are observed. It is considered epicardial fat to increase cardiovascular risk. Currently, there is no standardized methodology for measuring the thickness of the epicardial fat. As the most accessible method, the method of transthoracic echocardiography is considered and described.

Key words: epicardial fat, cardiovascular disease, cardiovascular risk, echocardiography.

Obesity, which has received the status of a non-communicable pandemic of the 21st century, is becoming one of the main public health problems, contributing significantly to premature mortality, increasing the cost of medical care and worsening the quality of life of patients. According to the multicenter observational study ESSE-RF, in 2012-2013 the prevalence of obesity in the Russian population reaches almost 30%, our country ranks fourth in the world in terms of the number of obese persons.

The results of numerous studies have shown that visceral fat is a hormonally active tissue that produces a large number of biologically active substances - adipokines involved in the development of metabolic disorders, inflammation and fibrosis, thrombus formation and atherogenesis, and the severity of VAT and the degree of its dysfunction are a key factor determining the nature of the obesity phenotype: complicated ("metabolically unhealthy") or uncomplicated ("metabolically healthy") obesity.

Epicardial adipose tissue (EFT) is located between the myocardium and the visceral pericardium, mainly behind the free wall of the right ventricle, in the atrioventricular and interventricular grooves, accounting for about 20% of the total weight of the ventricles of the heart, is of mesodermal origin and is supplied by the branches of the coronary arteries. Characteristic is the absence of the fascia separating the EFT and the underlying myocardium, which determines the presence of a single microcirculation system. EFT is a source of various biologically active substances that can affect the myocardium and coronary arteries through paracrine and vasocrine secretion.

Among them, pro-inflammatory and atherogenic adipokines are distinguished (tumor necrosis factor-α, monocytic chemotactic protein-1, interleukins (1, 1β, 6, 8), plasminogen activator-1 inhibitor, phospholipase-A2 of the second type, mitogen-activated protein kinase, chemokine, secreted by T-cells upon activation, intercellular adhesion factor, P-selectin, E-selectin and others), VAT markers (leptin, resistin, omentin, visfatin), profibrotic adipokines (activin A, transforming growth factor-β1), growth factors and remodeling of the heart and blood vessels (angiotensin-II, angiotensinogen, vascular endothelial growth factor, nerve growth factor), thermogenesis factors (uncoupling protein-1), as well as anti-inflammatory adipokines (adiponectin, adrenomedullin).

At the same time, the level of expression of most adipokines by adipocytes of epicardial fat is much higher than that of other visceral fat depots. EFT adipocytes also differ in size compared to adipocytes of subcutaneous fat and other visceral fat depots, a higher rate of uptake and release of free fatty acids, the excessive accumulation and oxidation of which in various pathological conditions can lead to the development of the phenomenon of "lipotoxicity".

The Framingham Heart Study and the Multi Ethnic Study of Atherosclerosis announced that ECF volume is an independent predictor of the risk of coronary heart disease (CHD). T. Mazurek et al. published data indicating the pro-inflammatory effect of ECF. Having studied biopsies of subcutaneous adipose tissue and ECF of patients with coronary artery disease who underwent coronary artery bypass grafting, the researchers found that the expression of proinflammatory cytokines in ECF is several times more pronounced than in subcutaneous adipose tissue. In addition, it was found that in the ECF of patients with progressive coronary artery disease, there are more proinflammatory macrophages of the M1 type (classically activated) and fewer anti-inflammatory macrophages of the M2 type (alternatively activated) compared with persons without coronary artery disease. The researchers suggested that the absence of the fascia separating the adventitia of the coronary arteries from the ECF may contribute to atherosclerotic lesions of the coronary arteries to a greater extent due to the paracrine effect of the ECF itself than from the processes of the systemic inflammatory process. One of the newest directions in the study of ECL is the study of the effect of drug therapy, in particular some antidiabetic drugs and statins, on the severity of ECI. Thiazolidinediones increase tissue sensitivity to insulin by acting on adipose tissue, muscle and liver, where they increase glucose utilization and decrease glucose synthesis. Sacks et al. Pioglitazone therapy was associated with a lower expression of pro-inflammatory genes, in particular interleukin-1b, in the ECF in patients with type 2 diabetes (DM 2) and coronary artery disease. In another study, it was shown that an agonist of g-receptors activated by peroxisome proliferators, rosiglitazone, can induce rapid dissolution of ECF in experimental models. An analogue of glucagon-like peptide-1, liraglutide, in patients with diabetes mellitus 2 and obesity led to a significant decrease in the thickness of the ECF according to echocardiography from 10.2 ± 2 to 6.9 ± 1.9 mm after 12 weeks and to 5.8 ± 1. 9 mm ($p < 0.001$) after 24 weeks of therapy. The dynamics of the ECL did not depend on a decrease in body weight and an improvement in the glucose profile. In a study by S. Morano et al. similar data were obtained on a decrease in the thickness of the ECF after 12 weeks of therapy with liraglutide or exenatide in patients with diabetes mellitus 2. Methods of the "gold standard" for EFT imaging, which allow assessing both the thickness in different parts of the heart and the total volume, include MSCT and MRI. At the same time, these studies are characterized by laboriousness, the need for specially trained personnel, high cost and, in the case of MSCT, radiation exposure for the patient, which significantly limits the possibility of their widespread use in clinical practice to assess the severity of epicardial obesity. In 2003 Iacobellis G, et al. first described a method for quantifying EFT using transthoracic echocardiography. The thickness of the epicardial fat, which is visualized as an echo-negative space between the free wall of the right ventricular myocardium and the visceral layer of the pericardium, was determined perpendicular to the free wall of the right ventricle in B-mode (parasternal position, along the long axis of the left ventricle), at the end of the systole along the line as perpendicular as possible the aortic ring (the site of origin of the ascending aorta), which was used as an anatomical landmark. The authors of the method proposed to evaluate this indicator at the end of the ventricular systole, since during diastole the compression of the EFT leads to an underestimation of the EFT value, and also complicates its differentiation from the pericardial adipose tissue located outside of the parietal pericardium. Subsequently, the presence of a high correlation between the echocardiographically determined TED and the volume of EFT according to MRI data was demonstrated (0.91, 1, with the amount of abdominal IVT according to MSCT data, as well as the amount of intramyocardial fat measured using proton magnetic resonance spectroscopy (0.79 , $p = 0.01$), which gives grounds to consider this indicator as a marker of both epicardial obesity and visceral obesity in general. It should be noted that

numerous clinical studies have shown differences in the average values of echocardiographically determined EAT in individuals without metabolic disorders and CVD, depending on ethnicity, indices of indirect evaluation of TD, as well as the age of patients, which suggests the presence of determinants of the indicator, which should be taken into account when determining the threshold values of the EAT as a criterion for epicardial (visceral) obesity.

Thus, in the course of the population prospective cohort study The Heinz Nixdorf Recall Study (n = 4093, 47% of men, average age of patients 59.4 years, follow-up period was 8.0 ± 1.5 years), it was shown that the frequency of fatal and non-fatal cardiovascular events increased with an increase in the volume of EFT according to MSCT data, amounting to 0.9% and 4.7% for the value of EFT in the first and fourth quartiles, respectively ($p < 0.001$), while doubling the volume of EFT was associated with a 1.5-fold increase CVD risk regardless of traditional CVR factors. The same study revealed the relationship of EFT with the dynamics of coronary artery calcification based on a two-fold analysis of the coronary calcium index, performed with a five-year interval. An increase in the volume of EFT by one standard deviation was accompanied by an increase in the indicator by 6.3% (95% CI 2.3-10.4%, $p = 0.0019$). In CVD-asymptomatic individuals with obesity verified on the basis of BMI and / or central (abdominal) obesity verified on the basis of threshold values for OT, the experts of the European Society of Cardiology consider it appropriate to conduct a systematic assessment of CVR, suggesting an assessment as a basic stratification tool. risk on the SCORE scale. At the same time, both obesity by BMI and central obesity are considered in these recommendations as factors that increase the initially determined risk on the SCORE scale. Currently, the most accessible method for verifying visceral obesity is the diagnosis of epicardial obesity based on echocardiographic evaluation of TEF according to the method described above. To establish the threshold value of this indicator, taking into account the presence of an association with various factors (determinants) (age, BMI, ethnicity, and others), additional research is needed, possibly within the framework of an appropriate register. At the same time, on the basis of the already available research results, the following TEF values can be proposed as a criterion for epicardial (visceral) obesity: ≥5 mm for people under 45 years old, ≥6 mm for people from 45 to 55 years old, ≥7 mm for people older 55 years. Currently, there is no threshold value for the thickness of the EFT. In the literature, there are many contradictions regarding the thickness of the EFT and the degree of its influence on the progression of cardiovascular diseases. It seems interesting that the thickness of the EFT, measured during the end systole, is a minimum of 1.1 and a maximum of 22.6 mm, with an average value of 7 mm in men and 6.5 mm in women (in healthy volunteers). When measured at the end of diastole, the mean value of the EFT thickness was 6.4 mm (1.1–16.6 mm) in patients with coronary artery disease and 4.7 ± 1.5 mm in asymptomatic patients. EFT thickness, measured at the end of diastole, more than 5 mm is considered as an independent predictor of the development of subclinical atherosclerosis, metabolic syndrome, low coronary reserve and hypertension. At the same time, the indicated value of the EFT thickness cannot be considered as a threshold value, since this has not been studied in large multicenter studies. When interpreting the obtained values of the EF thickness, it should be borne in mind that the EGT thickness can be influenced by age, gender, race, and in what phase of the cardiac cycle the measurement was performed. In addition, it should be remembered about a number of technical limitations of echocardiographic assessment of the EFT thickness, in particular, the greater interobserver variability compared to CT and MRI, as well as the transthoracic acoustic window, which limits the possibilities of EF visualization. Despite these difficulties, echocardiography remains the main method for measuring EFT. Echocardiographic determination of TED is undoubtedly important for secondary prevention in obese patients. In particular, in order to form a high-risk group of complications before carrying out planned myocardial revascularization, to identify a higher risk of CVC in patients undergoing acute coronary syndrome, to optimize preventive measures. In patients with atrial fibrillation, the assessment of EFT as an etiopathogenetic factor in the development of structural and functional atrial remodeling will be useful for resolving the issue of the volume of up-stream therapy of the disease.

Conclusion

EFT is a special visceral fat depot with unique anatomical and functional capabilities. It is an important source of biomolecules, which also serves as a secretory organ. EF thickness and volume can be measured using echocardiography, CT, or MRI. There is evidence that the volume and thickness of the EFT are associated with the degree and severity of metabolic syndrome and IHD, therefore, the measurement of the EFT thickness can be used as a prognostic marker of cardiometabolic diseases. Unfortunately, to date, there are no results of large population studies on the effect of EFT on the development and progression of ischemic heart disease. These studies are expected to lead to new therapeutic approaches for the treatment of cardiovascular disease.

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