Rev Port Cardiol. 2020;39(11):635–637

Revista Portuguesa de Cardiologia
Portuguese Journal of Cardiology
www.revportcardiol.org

EDITORIAL COMMENT

Epicardial adipose tissue (dys)function: A new player in heart disease?

(Dis)função do tecido adiposo epicárdico: um novo interveniente nas doenças cardíacas?

Paulo Matafome[a,b,c]

[a] *University of Coimbra, Coimbra Institute for Clinical and Biomedical Research (iCBR) and Institute of Physiology, Faculty of Medicine, Coimbra, Portugal*
[b] *University of Coimbra, Center for Innovative Biomedicine and Biotechnology (CIBB), Coimbra, Portugal*
[c] *Clinical Academic Center of Coimbra (CACC), Coimbra, Portugal*

Available online 2 November 2020

White adipose tissue is a highly active metabolic and endocrine tissue formed of adipocytes and the stromal vascular fraction (preadipocytes, mesenchymal progenitor cells, endothelial cells, pericytes, macrophages and fibroblasts). The crosstalk between these cell populations provides high dynamicity and plasticity in response to environmental changes and energy status. While insulin stimulates triacylglyceride (TAG) synthesis through sterol regulatory element-binding transcription factor 1c (SREBP-1c)-induced lipogenesis after meals, other factors like glucagon, cortisol, growth hormone and thyroid hormones stimulate the hydrolysis of stored TAGs into fatty acids and glycerol (lipolysis).[1] Lipid anabolism and consequent tissue expansion require dynamicity and plasticity of the vasculature, avoiding formation of hypoxic regions, which are usually associated with inflammation and fibrosis. Differentiation of preadipocytes into mature adipocytes (adipogenesis) occurs along the vascular wall, and angiogenesis is also regulated by adipocyte-derived factors, so that each adipocyte is irrigated by at least one capillary.[2] Thus, angiogenesis and adipogenesis are mutually regulated, in what may be called adipovascular coupling. Neovascularization is associated with increased adipocyte number (hyperplasia), while angiogenesis deficits are associated with larger adipocytes (hypertrophy).[2] The adipocyte secretome has been shown to shift from anti-inflammatory, angiogenic and matrix remodeling factors of smaller and irrigated adipocytes, to proinflammatory cytokines, chemokines and profibrotic factors of hypertrophic adipocytes (hepatocyte and fibroblast growth factors, transforming growth factor beta, tumor necrosis factor alpha and matrix metalloproteinases). These conditions are also associated with an imbalance in angiogenic factors, which leads to alterations in vascular architecture, chronic hypoxia, propagation of the proinflammatory milieu and impairment of other adipokines, such as adiponectin, leptin and resistin.[1]

Epicardial adipose tissue (EAT) is located between the visceral layer of the pericardium and the myocardium,

DOI of original article:
https://doi.org/10.1016/j.repc.2020.03.017
E-mail address: paulomatafome@gmail.com

https://doi.org/10.1016/j.repc.2020.10.001

while pericardial adipose tissue is located outside the pericardium. Moreover, EAT is irrigated by the coronary circulation, while pericardial adipose tissue is not, and EAT may also be found around coronary arteries, which may directly influence coronary blood flow. This fat depot is especially rich in preadipocytes, rather than mature adipocytes, and shares some features with brown and beige adipocytes, including UCP1 expression and a higher metabolic rate than other fat pads. EAT has a higher capacity for uptake and release of fatty acids, which is important to sustain myocardial metabolism in physiological conditions. Fatty acid flux is regulated by vasoactive factors released by EAT, which control coronary vessel tone. Besides providing fatty acids for cardiomyocyte metabolism, EAT also protects the myocardium through its mechanical and thermogenic properties, preventing changes in myocardial structure and temperature during contraction.[3]

EAT is easily detected by common imaging methods such as ultrasonography or computed tomography, which enable its volume to be measured with high accuracy. The relationship between EAT volume and cardiovascular function has been examined in a large number of studies. EAT volume has been correlated with several features of coronary artery disease, including coronary calcification, carotid intima-media thickness and coronary flood flow in patients with coronary artery disease but normal myocardial perfusion.[4] EAT volume was also correlated with poorer left ventricular diastolic function, but not other parameters of ventricular function.[5]

Reduction of EAT volume through physical exercise and sleeve gastrectomy was recently proposed as a promising strategy to reduce atherosclerotic lesions, due to reductions in proinflammatory adipokines and improvement of the inflammatory milieu in the coronary vessel wall.[6] Moreover, GLP-1 receptor expression in EAT was recently shown to be linked to genes involved in fatty acid oxidation, and liraglutide was observed to produce a marked decrease in this fat depot.[7]

The study of EAT is not a simple task because, besides the fact that its collection requires invasive thoracic surgery, it is not found in rodent models. Moreover, EAT is often obtained from chronic patients undergoing surgery, which does not provide information about early metabolic and endocrine alterations of this fat depot. Thus, factors including difficult access, duration of metabolic or cardiac disease and medication may hamper study of the mechanisms linking EAT (dys)function with cardiac disease.

The role of other fat depots was initially reported in the context of the pathophysiology of metabolic syndrome, body mass index (BMI) and adiposity being considered the main risk factors for insulin resistance and glucose intolerance. Nowadays, several years after the first studies, there is a growing body of evidence showing that BMI is not a good predictor of metabolic disease, especially insulin resistance. Instead, various studies have reported that adipose tissue dysfunction, with changes in metabolic and endocrine functions, is more closely associated with insulin resistance-associated diseases, such as type 2 diabetes and non-alcoholic fatty liver disease. Thus, EAT can be expected to undergo various changes in metabolic syndrome, which may be related to its greater proatherogenicity. EAT from type 2 diabetic patients was shown to present infiltration of immune cells (including macrophages, T lymphocytes and dendritic cells) and impaired expression of key genes, with a more proinflammatory profile. This inflammatory infiltration creates a proinflammatory environment that extends to the surrounding vessels and cardiomyocytes. The correlation between EAT volume and changes in systolic and diastolic function was observed to be stronger in type 2 diabetic patients than in controls, suggesting that changes occurring in EAT in type 2 diabetes directly impact myocardial function.[8]

From an imaging standpoint, good markers of EAT infiltration are necessary. Recently, a study by Liu et al. showed that changes in attenuation, calculated from cardiac computed tomography angiography, are a better predictor of atherosclerosis than EAT volume by itself.[9] In molecular terms, impaired EAT secretion of adipokines and profibrotic factors has been observed,[10] but little is known regarding the molecular links between EAT (dys)function and cardiovascular function.

Thus, although there is currently some evidence that EAT may be associated with coronary artery disease and other cardiac disease, there is a need for studies able to dissect the molecular links between EAT (dys)function and cardiac disease. In this issue of the *Journal*, Mancio et al. describe the protocol of a study aiming to identify new mechanisms of EAT dysfunction with the potential to become new therapeutic targets in cardiac disease.[11] In particular, application of state-of-the-art high-throughput proteomic methods and their correlation with cardiac function parameters have the potential to open up new paths to the identification of new early surrogate markers of cardiac disease.

Conflicts of interest

The author has no conflicts of interest to declare.

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