Editorial / Editöryal Yorum

Epicardial fat: More than an adipose tissue

Epikardiyal yağ: Bir yağ dokusundan daha fazlası

Göksel Çinier M.D., [ID]¹ **Sanem Nalbantgil M.D.** [ID]²

¹Department of Cardiology, Dr. Siyami Ersek Thoracic and Cardiovascular Surgery Training and Research Hospital, İstanbul, Turkey
²Department of Cardiology, Ege University School of Medicine, İzmir, Turkey

Only little was known until recently about the function of the tiny fat tissue located between visceral pericardium and epicardium of the heart. The terminology epicardial adipose tissue (EAT) is used to differentiate it from the paracardial adipose tissue and to highlight the close anatomical intimacy with the underlying cardiac muscle. This unique localization allows EAT to mediate its local and systemic functions which have distinct consequences particularly on cardiac tissue. The curve of the research interest for EAT has been upraised following the fact that traditional obesity parameters including body mass index (BMI), waist circumference and total body fat mass have been frequently found as only crude indicators for being "metabolically healthy." Although there is still an ongoing debate among researchers, the term "obesity paradox" has been emerged following the evidence that some patients who are above the upper limit of BMI had lower cardiovascular morbidity and mortality compared to those who are within normal BMI range.[1] This led to paradigm shift from traditional anthropometric measurements to visceral adiposity for being the major determinant of cardiovascular health.

Advances in imaging technologies enabled quantification and analysis of the visceral adiposity in different locations such as intrahepatic, peripelvic and epicardial areas. For several decades researchers asked the same questions; "what are the role of these adipose tissues on particular organs and systems?", "are their role unfavourable, protective or both?", "what are major triggers for their activation?". Following substantial studies, we now can answer some of those questions.

Under normal conditions EAT acts as a regulator of vascular flow by vasocrine mechanisms, protector of myocardium and coronaries from inflammatory cells, source of fatty acids for myocardium, barrier for mechanical stress and provides multipotent progenitor cells.[2] Through releasing adiponectin, EAT exerts beneficiary effects on cardiovascular system by reducing vascular tonus, preventing remodelling and counteracting pro-inflammatory mediators. However, in the dysfunctional state, recent evidence suggest that EAT acts as a local mediator of systemic inflammation. It is still remained to be elucidated what triggers and through which mechanisms activation of structural and functional changes occur in EAT during pro-inflammation. Conditions such as obesity, insulin resistance, diabetes and chronic inflammatory diseases induce shift in EAT toward pro-inflammatory phenotype characterized by secretion of several cytokines and chemokines resulting in infiltration of inflammatory cells and fibrosis. The most prominent feature of EAT is the absence of any layer between underlying epi-

Abbreviations:	
AF	Atrial fibrillation
AUC	Area under curve
BMI	Body mass index
CRP	C-reactive protein
EAT	Epicardial adipose tissue
ECG	Electrocardiography
IL-6	Interleukin-6
LA	Left atrium
NSTEMI	Non-ST segment elevation myocardial infarction
TNF-α	Tumor necrosis factor-α
TTE	Transthoracic echocardiography

Correspondence: Göksel Çinier, M.D. Department of Cardiology,
Dr. Siyami Ersek Thoracic and Cardiovascular Surgery Training and Research Hospital, İstanbul, Turkey
Tel: +90 532 484 23 50 e-mail: cinierg@gmail.com

cardium which facilitates its effect on the progression of myocardial structural and electrical remodelling.

The causality link between atrial fibrillation (AF) and EAT has been investigated in recent studies.[3] Evidence suggested that higher EAT volume (quantified by cardiac computed tomography or magnetic resonance imaging) or thickness (assessed by transthoracic echocardiography [TTE]) was not only associated with prevalent AF but also predicted new-onset AF, arrhythmia burden and recurrence following rhythm control.[4-6] More importantly the relationship between EAT and elevated AF risk remained significant even after adjustment for common AF risk factors such as, increased age, hypertension, heart failure and obesity. We knew before that systemic pro-inflammatory state elevates the risk of AF development, but could EAT be really the local mediator of this process? Serum concentrations of the systemic pro-inflammatory biomarkers including C-reactive protein (CRP), interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) increase in patients with AF. Interestingly these biomarkers are found abundantly in EAT samples among patients with AF. Furthermore, inflammatory activity of EAT as evidenced by increased uptake of 18-fluorodeoxyglucose detected by positron emission tomography was significantly higher in patients with AF compared to the control group.[7] EAT in the vicinity of the left atrium (LA) is the most active site which is in accordance to the current AF pathogenesis. Volume of EAT is also associated with adipocyte infiltration to the adjacent myocardium. Histopathological studies elegantly demonstrated significant adipocyte infiltration in posterior LA wall correlated with higher EAT volume particularly in persistent AF. These findings correspond to the electrical heterogeneity in this group of patients as evidenced by low bipolar voltage areas and fractionated potentials during electroanatomical mapping of posterior LA.

In this issue of the journal Eren et al.[8] investigated the predictive value of EAT for incident AF during in-hospital follow up among patients with non-ST segment elevation myocardial infarction (NSTEMI). They retrospectively analyzed the data from 494 patients who underwent angiography for NSTEMI. EAT was determined by TTE. Among included patients 68 (14%) developed AF in-hospital. Basal characteristics were similar between groups except prevalence

of diabetes and peak troponin level were higher in patients with AF. Angiographic data showed more severe coronary disease in AF patients as indicated by higher TIMI risk scores. Not surprisingly EAT thickness was higher in patients who developed AF compared to those who did not (8.3 mm±2.0 mm vs 6.1 mm±2.1 mm). Logistic regression analysis revealed EFT predicted new onset AF during in-hospital period [OR 3.521, 95% CI (1.616-6.314), <0.001] and EFT thickness of more than 6.5 mm had 72% and 77% sensitivity respectively for predicting AF with the area under curve (AUC) of 0.762.

These results expanded the evidence for the interlink between EAT and new onset AF but caution is needed when interpreting the results. First, underlying mechanisms for new onset AF in the context of acute ischemia might be different from what we know as well-known risk factors for AF. Indeed, coronary artery disease increases the risk for AF but this mostly accumulates during long term. AF that develops during hospitalization period often related to the ischemia in atrium, sinus node and atrioventricular node arteries and more likely develops in the setting of right ventricular myocardial infarction. Thus, more angiographic data is needed for drawing conclusion in this regard. Second, timing, definition and diagnostic methods for AF are inconclusive. Very early incident AF might well be regarded as reperfusion arrhythmia or might occur secondary to catheter manipulation which could not be inferred to EAT. Generally, the cut-off duration for AF for the diagnosis is 30 seconds but the exact definition of AF is missing in the text. More importantly, as authors mentioned in the limitation part, AF episodes were diagnosed with 6-hour electrocardiography (ECG) recordings and they received further rhythm monitoring in case they had symptoms. However, we do not have the information at which time period did patients undergo ECG monitoring and how many of the episodes were asymptomatic. Given the fact that symptomatic and asymptomatic AF episodes have different outcomes, this information is of value for clinical implication. Third, despite the fact that EAT determined by TTE is correlated with measurements with cardiac computed tomography and cardiac magnetic resonance imaging, there is increasing amount of evidence that EAT volume adjacent to the LA is the best indicator for AF occurrence.[9] Nevertheless, TTE seems the best modality when considering cost effectiveness and

availability but it should be kept in mind that inter- and intra-observer variability and blindness to other clinical data when performing TTE is of utmost importance. Finally, the incident AF was diagnosed in 14% of included patients which seems to be higher compared to what were found in similar studies.[10,11] This is interesting and needs further explanation as patients with high risk features for AF such as prior AF, chronic kidney disease, coronary artery disease, ST-segment elevation myocardial infarction, previous stroke and heart failure were excluded from the study. Possible explanations causing this high incident rate, which are not given in the manuscript, are failure of percutaneous coronary intervention, inclusion of asymptomatic episodes or lack of guideline directed medical therapy.

Despite these limitation authors should be congratulated for executing this important study and for their new findings. It seems that EAT will still be the focus point for future research and more evidence is needed for understanding the functions and clinical implications of this tiny adipose tissue. More importantly, new therapeutic approaches such as SGLT-2 inhibitors should be tested in large and well-designed randomized clinical trial to determine possible solutions for preventing deteriorating effects of EAT on cardiac tissue.

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