Epicardial adipose tissue: Just a predictor or a local player for coronary atherosclerosis?

Recently there has been increasing interest on the possible link between epicardial adipose tissue (EAT) and several cardiovascular diseases (1). The relationships between the amount of EAT and risk of coronary atherosclerosis, atrial fibrillation, heart failure and coronary microvascular dysfunction have been shown in previous studies (1). An accurate estimate of the thickness or the total volume of epicardial fat is readily available from various imaging techniques including echocardiography, cardiovascular magnetic resonance and cardiac computed tomography which makes EAT an appealing parameter to be incorporated into clinical risk stratification for these conditions. Role of EAT as a clinical predictor and risk factor has been studied most extensively in coronary atherosclerosis (1-3). Studies have also shown that EAT may not be only a predictor for atherosclerosis but may also play a direct local role in the pathogenesis of atherosclerosis (4, 5). If this hypothesis holds true imaging EAT may be even more promising as it may be a direct target for decreasing risk of coronary atherosclerosis.

EAT is located between the myocardium and the visceral pericardium and is in direct continuity with the myocardium (6). There is no fascia or tissue separating the EAT and the myocardium and EAT may extend to the underlying myocardium (6). The interest on EAT as a predictor for coronary atherosclerosis perhaps first originated from the idea that it could be representative of visceral adiposity and as such may be a marker for metabolic syndrome and a source of systemic adipokines involved in atherosclerosis. Indeed many studies have shown clear link between EAT thickness/volume with components of metabolic syndrome and coronary atherosclerosis (1, 2). The main question that arises then is whether EAT is an independent predictor for coronary atherosclerosis or it is just a reflection of general visceral obesity. In large cohort studies EAT has been shown to be significantly related to components of metabolic syndrome and risk factors for coronary atherosclerosis, however most of these relations lost significance when visceral adiposity was entered in the analysis (1). However there are also studies that showed independent contribution of EAT for prediction of coronary atherosclerosis and cardiac end points. Shmilovich et al. (7) defined the upper normal range of EAT volume in a normal population and then assessed predictive role of increased EAT volume on major cardiovascular events in a cohort of patients with 4 years of follow-up. They found that EAT volume emerged as an independent risk predictor for major cardiovascular events also with a trend of additive value to coronary artery calcium and Framingham risk scores in risk prediction. In fact, the results of this study is indirectly suggesting some possible local effects of EAT on coronary arteries.

The very close proximity of EAT to the myocardium and coronary arteries suggests that EAT may have a direct and local role in the pathogenesis of coronary atherosclerosis. EAT not only covers the myocardium from outside but also totally encases the coronary arteries forming a part of their adventitia. Moreover, the coronary artery adventitia and the EAT share the same microcirculation system. These anatomical relations and proximity suggest that EAT may have a local effect on the coronary arteries. Early studies have shown that EAT is not a dormant fat tissue but in fact is very active and may be a source of inflammatory mediators. Mazurek et al. (4) demonstrated that EAT samples derived from patients undergoing coronary artery bypass surgery showed significantly high expression of several inflammatory markers and this was accompanied by dense inflammatory cellular infiltration. Interestingly the degree of inflammation in the EAT seen was not reflected in the serum inflammatory biomarkers in this study. Similar findings were reported by Baker et al. (5) who showed that expression of inflammatory cytokines in the EAT from patients with coronary artery disease was comparable to expression of these in the visceral abdominal fat, suggesting role of EAT as a local resource for these cytokines. Chatterjee et al. (8) studied gene expression profile of perivascular adipose cells from non-diseased blood vessels and found out that these cells are markedly less differentiated and small adipose cells with increased expression of inflammatory genes and decreased expression of anti-inflammatory adipokines. In the mouse model of their experiments they have demonstrated that with only two weeks of high fat feeding these cells acquired even less differentiated from of adipocytes with exacerbated inflammatory gene upregulation. All these studies are suggesting that EAT may play an important dynamic role in local perivascular inflammation and may potentially contribute to inflammatory milieu typical of coronary atherosclerosis. These observation have backboned the "outside-to-inside" hypothesis of atherosclerosis in addition to the classical understanding of atherosclerosis as an intimal disease.

So, if EAT has a local role in the pathogenesis of atherosclerosis as studies in tissue samples suggest, then targeting the

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EAT may be a realistic approach for decreasing the risk of atherosclerosis. Supporting this idea, a recent study by Alexopoulos et al. (9) has shown that EAT regresses with intensive statin therapy independently of decrease in low density lipoprotein levels. In another study pioglitazone and simvastatin have been shown to favourably alter the inflammatory and adipokine profile of EAT (10). While further studies are needed to show the effectiveness of treatment approaches aiming at EAT for decreasing risk of coronary atherosclerosis at the same time we need more clinical evidence proving that EAT indeed has a local role in coronary atherosclerosis. To this end, clinical studies on local effects of EAT are much less in number compared to studies relating EAT to overall risk of coronary artery disease. Perhaps the most simple evidence on the local role of EAT comes from the observation that coronary artery segments following an intra-myocardial course and hence have no direct contact to EAT, i.e. muscular bridges, are exceptionally free of atherosclerosis (11). There is also at least one anatomical and one functional clinical study showing the relationship between presence of coronary atherosclerosis and local EAT (12, 13). Mahabadi et al. (12) divided left anterior descending and circumflex arteries into segments and assessed presence of calcified and non-calcified plaques in each segment in relation to EAT volume of the segment. They have found a significantly increased risk of presence of coronary plaque with increasing volume of EAT over that segment and the significance were preserved after adjustment for conventional cardiovascular risk factors. Khawaja et al. (13) studied regional epicardial fat in relation to reversible myocardial perfusion defect in all the three coronary territories. They have reported that inducible myocardial perfusion defects were associated with significantly higher local EAT volume in the right and left coronary artery distributions (13). Periaortic fat, which has very similar characteristics to the EAT, has been shown to be an independent predictor of thoracic aorta dimensions in a large community based study of the Framingham offspring cohort (14). All these studies provide some evidence that local effects of EAT may have clinical relevance when evaluating coronary atherosclerosis in clinical practice.

In this issue of the *Anatolian Journal of Cardiology*, Çullu et al. (15) are presenting the results of their study on EAT volumes in relation to presence of plaques in the three coronary arteries assessed by coronary computed tomography. As would be expected from the results of previous studies EAT volume was significantly higher in patients with coronary plaques. They have assessed the total EAT volume in patients with plaques in different coronary arteries and found out that patients with multivessel, left anterior descending and right coronary artery plaques had higher EAT volumes compared to patients with plaques in the circumflex artery or no plaques at all. Although they did not specifically correlate the location of EAT to the location of the coronary artery segment with plaques, the results of this study still adds on the limited data about possible local effects of EAT. Interestingly, lower total EAT volumes in patients with circumflex artery plaques may also be a supporting proof for the local effects of LAT. While it may appear paradoxical, left atrioventricular groove where circumflex artery courses is a prominent location for EAT and just local accumulation of EAT in this area without increasing the total EAT volume may have a local causative role in circumflex atherosclerosis.

Much is still required for a better understanding of the role, particularly the local role, of EAT in coronary atherosclerosis for it to be a candidate target for decreasing risk of coronary artery disease. Until then it still holds clinical utility as an easily available proxy marker for visceral adiposity and general systemic atherosclerotic milieu.

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