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Roles of Epicardial Adipose Tissue in the Pathogenesis of Coronary Atherosclerosis

— An Update on Recent Findings —

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Adipose tissue serves not only as an energy store or a mechanical cushion, but also as an endocrine organ. Recent evidence revealed that perivascular adipose tissue is involved in vascular homeostasis and pathophysiology of adjacent arteries by producing various adipokines. Epicardial adipose tissue (EAT) is located between the surface of the heart and the visceral layer of the pericardium and surrounds the coronary arteries. Many clinical studies suggest that an increase in EAT volume is associated with coronary artery disease. It has been reported that exercise and some antidiabetic drugs can reduce EAT volume. In this review, we outline recent findings on the roles of EAT in the pathogenesis of coronary atherosclerosis.

Key Words: Adipose tissue; Atherosclerosis; Inflammation

Most of arteries, except for cerebral arteries and microvessels, are surrounded by perivascular adipose tissue (PVAT).[1] Although it has been considered that PVAT functions as a supporting tissue and a mechanical cushion for the vasculature, recent studies have shown that PVAT secretes adipokines, including inflammatory cytokines and chemokines, such as interleukin (IL)-1β, IL-6, tumor necrosis factor (TNF)-α, monocyte chemoattractant protein-1, and adiponectin. PVAT also secretes nitric oxide, reactive oxygen species, and angiotensin II, consequently regulating vascular homeostasis and reactivity (**Figure 1**).[2,3]

Inflammation in the PVAT leads to the production of inflammatory cytokines, which potentially play an important role in the pathophysiology of atherosclerosis.[4–6] We previously investigated the effects of PVAT on neointima formation after mechanical endovascular injury.[7] In healthy mice, removal of PVAT markedly enhanced lesion formation, which was attenuated by transplantation of subcutaneous adipose tissue from mice fed regular chow. Diet-induced obesity causes inflammatory changes in PVAT, and this is associated with enhanced lesion formation.[8] Together, these results indicate that obesity causes inflammation in the PVAT and exacerbates lesion formation, whereas PVAT is atheroprotective under healthy conditions.[8,9]

Epicardial adipose tissue (EAT) is located between the surface of the myocardium and the visceral layer of the pericardium, surrounding coronary arteries (**Figure 2**). EAT is anatomically close to the myocardium. EAT and the myocardium are believed to share the same microcirculation.[10] Anatomically, epicardial and paracardial adipose tissues are quite different.[11,12] Paracardial fat is adherent and superficial to the parietal layer of the pericardium without direct connection with coronary arteries. The pericardium must be precisely identified in order to quantify EAT volume.[10,13,14] The combination of epicardial and paracardial fat components is called "pericardial fat". Some researchers use the term "pericardial fat" for paracardial fat.[10,13,14]

Many clinical studies suggest that an increase in EAT volume is associated with coronary artery disease (CAD).[15–18] We also reported that inflammation is enhanced in the EAT of patients with CAD,[19,20] suggesting that EAT plays a crucial role in the pathogenesis of coronary atherosclerosis.[4,21] In this review, we discuss recent findings regarding the role of EAT in the pathogenesis of coronary atherosclerosis.

EAT Quantification and Risk of Cardiovascular Diseases

It has been reported that EAT volume or thickness is associated with the presence and severity of CAD.[21] A prospective study of a general population of 4,093 people reported that EAT volume was associated with fatal and non-fatal coronary events independent of traditional coronary risk factors over a mean (±SD) 8.0±1.5 years of observation.[22]

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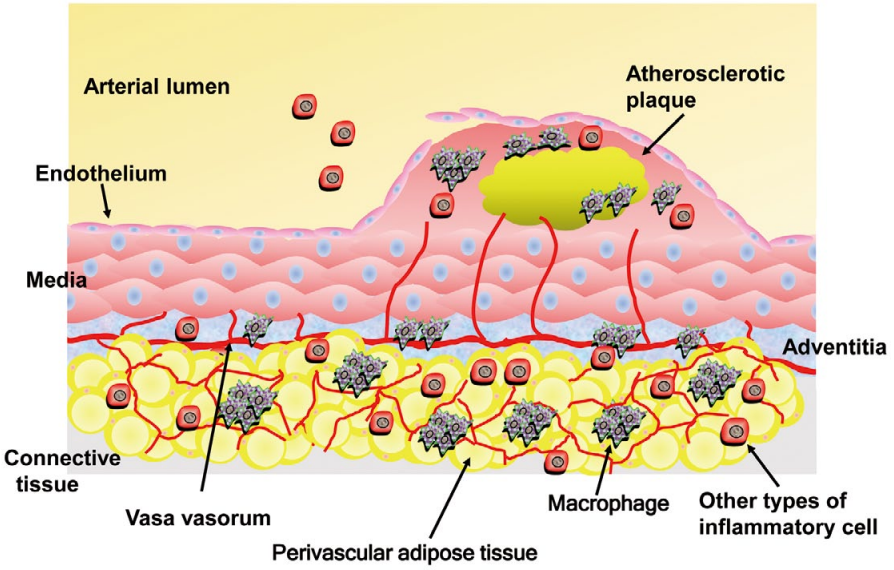

Figure 1. Atherosclerotic lesion and perivascular adipose tissue (PVAT). PVAT secretes various adipokines that regulate vascular homeostasis and reactivity. Inflammation in PVAT leads to the production of inflammatory cytokines, which potentially play an important role in the pathophysiology of atherosclerosis. At the site of the atherosclerotic lesion, the vasa vasorum proliferates and invades into the lesion from the adventitia. Secreted humoral factors and inflammatory cells reach the adjacent arterial wall by direct infiltration or via the vasa vasorum.

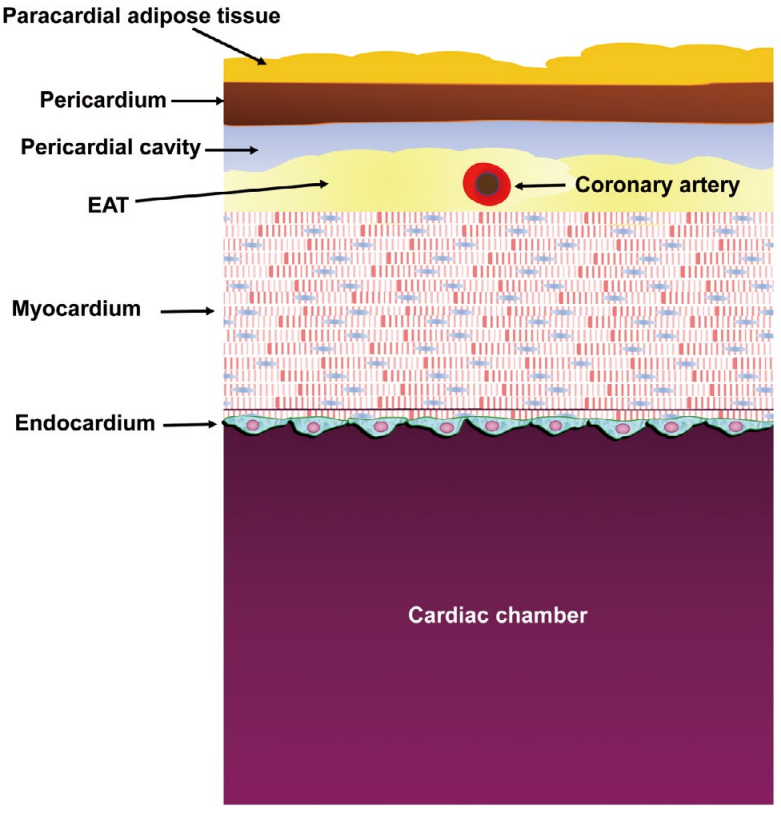

Figure 2. Epicardial adipose tissue (EAT) and paracardial adipose tissue. The EAT is located between the surface of the myocardium and the visceral layer of the pericardium, surrounding the coronary arteries. The EAT is anatomically close to the myocardium. Paracardial adipose tissue is adherent and superficial to the parietal layer of the pericardium, without direct connection with coronary arteries. Anatomically, the EAT and paracardial adipose tissue are quite different. The pericardium needs to be identified precisely to quantify the EAT. The combination of epicardial and paracardial fat components is called "pericardial fat". Some researchers use the term "pericardial fat" for paracardial fat.

After this study, many prospective studies examined the relationship between EAT volume and the onset of CAD events. For example, Commandeur et al evaluated the performance of machine learning, integrating clinical parameters with coronary artery calcium and automated EAT quantification, for the prediction of the long-term risk of myocardial infarction (MI) and cardiac death in asymptomatic subjects and found that the machine learning method significantly improved the prediction of MI and cardiac death compared with standard clinical risk assessment.[23] It was also reported that fully automated EAT volume and attenuation (Hounsfield units) quantification by deep learning from non-contrast cardiac computed tomography (CT) can provide prognostic value for asymptomatic patients.[24] EAT thickness measured by echocardiography was associated with the composite endpoint of non-fatal cardiovascular events (coronary revascularization, MI, heart failure, cardiac arrest, cerebrovascular disease, and peripheral artery disease) and all-cause mortality in patients with type 2 diabetes (T2D), particularly in men, after adjusting for cardiovascular disease (CVD) risk factors.[25] EAT modestly improved risk prediction over conventional CVD risk factors. In addition, it was reported that the superior interventricular groove, an index of the thickness of EAT, obtained from cardiac magnetic resonance imaging (MRI) measurements performed within 1 week after revascularization in patients with ST-elevated MI was a predictor of major adverse cardiovascular events independent of on age, sex, and left ventricular ejection fraction, among others.[26]

EAT quantification may be used for risk stratification for CVD in addition to other conventional risk factors.

Relationship Between Increased EAT Volume and Abdominal Visceral Fat Accumulation

Many studies have reported that visceral abdominal tissue (VAT) is associated with CVD and its risk factors, including diabetes, insulin resistance, hypertension, and dyslipidemia.[27] VAT is reported to be associated with plaque morphology.[28] By analyzing participants free of CVD in the Framingham Heart Study, Rosito et al reported that pericardial fat was correlated with multiple measures of adiposity and CVD risk factors.[27] VAT was a stronger correlate of most metabolic risk factors. Intrathoracic and pericardial fat were associated with vascular calcification, suggesting that these fat depots may exert local toxic effects on the vasculature.[27] Britton et al reported that visceral adiposity, but not pericardial fat, was associated with incident CVD after adjusting for clinical risk factors and generalized adiposity in participants from the Framingham Heart Study.[29] In these analyses from the Framingham Heart Study, pericardial fat, but not EAT, was measured between 2002 and 2005 using multidetector CT (MDCT). It is plausible that the spatial resolution of MDCT at that time was not high enough to distinguish between EAT and paracardial fat by precisely identifying the pericardium.

Thus, it remains unknown whether EAT is more valuable than VAT in predicting CAD, because few studies have measured VAT and EAT volumes in the same subjects. Oikawa et al reported that echocardiographic EAT was an independent predictor of coronary calcification and coronary atheromatous plaque, but that abdominal VAT area was not.[30] Ueda et al measured paracardial, epicardial, visceral, and subcutaneous fat indices and found that the paracardial fat index was the most valuable for evaluating the presence or severity of CAD.[31] Conversely, Sato et al reported that among EAT, VAT, and subcutaneous fat, visceral fat is the strongest risk factor for cardiometabolic diseases, although epicardial fat accumulation may be a risk factor for coronary atherosclerosis in subjects without visceral fat accumulation.[32] Future studies should clarify relationship between EAT and VAT in the pathogenesis of CAD.

Imaging Techniques to Evaluate the Quality of EAT

EAT has been primarily quantified by volume measurement on CT or MRI, or by measuring its thickness using echocardiography. Increased accumulation of visceral fat was shown to be associated with enhanced inflammation in adipose tissue.[33] Like visceral fat, several studies reported that increased EAT volume was associated with enhanced inflammation in adipose tissues, as determined by histological and/or biochemical analysis of biopsy samples obtained during cardiac surgery.[15,16,19,20] A non-invasive way of estimating the quality of EAT has been wanted, but the EAT phenotype cannot be detected using common imaging modalities. However, new imaging techniques have recently been reported that can assess the inflammatory status of EAT.

Fat Attenuation Index (FAI)

It has been reported that inflammation in the pericoronary adipose tissue can be estimated using a novel analysis of conventional coronary CT angiography (CCTA).[34,35] The authors of those studies developed an imaging metric, the CT FAI, which reflects adipocyte lipid content and size. The method was validated by analyzing human EAT explants obtained during cardiac bypass surgery, and it was shown that the FAI was able to detect adipose tissue inflammation.[34] In a validation cohort study, the FAI gradient around human coronary arteries could identify early subclinical CAD and detect inflamed, vulnerable atherosclerotic plaques during acute coronary syndrome.[34] The authors claimed that atherosclerotic lesions in human coronary arteries exert paracrine effects on the EAT, affecting local intracellular lipid accumulation in preadipocytes that can be monitored using the pericoronary FAI.[34] The same group further investigated whether FAI in EAT can predict clinical outcomes, using post hoc analysis of outcome data gathered prospectively from 2 independent cohorts of consecutive patients undergoing CCTA.[36] Pericoronary FAI indicated inflammation in coronary arteries, and enhanced cardiac risk prediction and restratification over conventional risk factors.[36] This group also proposed a new artificial intelligence-powered method to predict cardiac risk by analyzing the radiomic profile of pericoronary adipose tissue.[37] FAI analysis using conventional CCTA images may become a new biomarker for CADs.

Positron Emission Tomography (PET)/CT

Fluorine 18-fluorodeoxyglucose (^{18}F-FDG) PET has assumed increasing importance in the diagnosis of infection and inflammatory diseases such as aortitis and sarcoidosis. In addition, ^{18}F-FDG PET has been reported as useful in assessing the inflammation of visceral adipose tissue.[38,39] It was considered that enhanced FDG uptake in human adipose tissue indicates increased glucose uptake due to

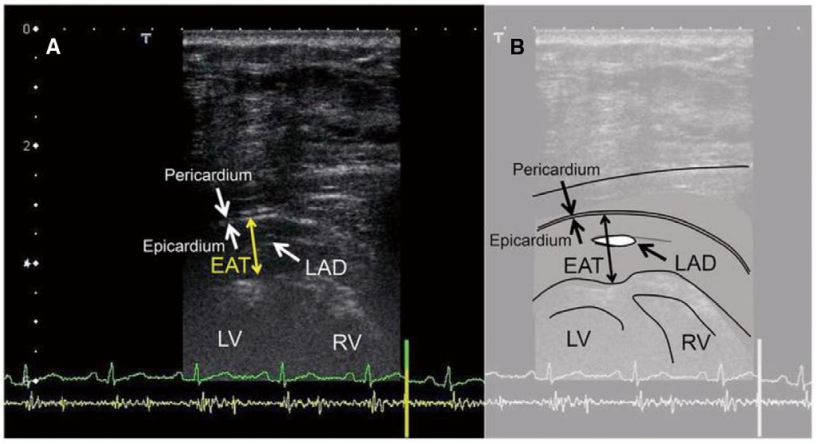

Figure 3. Representative echocardiographic image of epicardial fat tissue (EAT). (**A**) Measurement of epicardial fat thickness using a high-frequency linear probe. (**B**) Schematic illustration of the echocardiographic image. LAD, left anterior descending coronary artery; LV, left ventricle; RV, right ventricle. Reproduced from Yagi et al[50] without modification.

inflammation of adipose tissue.[38] In patients with CAD or multiple CAD risk factors, FDG uptake in neck subcutaneous, chest pericardial, and chest subcutaneous adipose tissue was significantly associated with FDG uptake in the adjacent arteries, carotid artery, and ascending aorta.[38] Weight gain was the most important risk factor for increasing FDG uptake by fat tissues.[39] FDG uptake, standardized by left atrial blood activity, also indicated that the inflammatory activity of pericoronary fat was greater than that of fat in other locations, such as subcutaneous fat and visceral fat, in patients with CAD.[40] Furthermore, the standardized uptake of FDG by pericoronary fat in CAD patients without a recent inflammatory reaction such as diabetes or a recent coronary intervention was greater than that in non-CAD controls, and was correlated with the extent of CAD.[40] However, this study had limitations, such as lack of motion correction.[41]

Electrocardiogram (ECG)-gated ^{18}F-FDG PET/CT enables more accurate evaluation of small structures of the coronary artery and perivascular tissue.[42] Using CCTA and ECG-gated ^{18}F-FDG PET/CT, Ohyama et al reported that coronary PVAT volume and coronary perivascular FDG uptake were significantly increased in patients with vasospastic angina.[42] That study indicated that inflammation of the coronary PVAT may be the cause of the vasospasm.[42]

Possible Treatments to Reduce EAT Burden

It is plausible that treatments to reduce EAT volume would ameliorate the inflammatory phenotype of EAT, suppressing the coronary atherosclerosis process. Several treatments to reduce EAT volume have been reported recently.

Exercise

Kim et al reported that aerobic exercise training significantly reduced EAT thickness in obese men.[43] The reduction in EAT was correlated with a decrease in visceral adipose tissue and the percentage changes in EAT and VAT were similar.[43] In another study, Kahl et al investigated the effects of exercise on adipose tissue compartments in patients with major depressive disorder, using MRI to measure the volume of subcutaneous adipose tissue, intra-abdominal adipose tissue, and EAT.[44] Exercise significantly reduced EAT, subcutaneous adipose tissue, weight, and body mass index (BMI); although there was a slight decrease in the volume of intra-abdominal adipose tissue, the difference was not statistically significant.[44]

It has been shown that IL-6 modulates fat metabolism in humans, increasing fat oxidation and free fatty acid re-esterification without causing hypertriacylglyceridemia.[45] IL-6 has been shown to stimulate myocardial hypertrophy in vitro and in vivo.[46] Christensen et al randomly assigned 52 abdominally obese but otherwise healthy participants to moderate- to high-intensity aerobic exercise or to no exercise, with or without monthly infusions of the IL-6 receptor antagonist tocilizumab.[47] Exercise significantly reduced EAT volume and increased cardiac muscle mass and the effects of exercise were abolished by tocilizumab, suggesting that exercise reduces EAT accumulation through IL-6 receptor-dependent lypolysis.[47]

A meta-analysis of 5 randomized controlled trials evaluated whether exercise or a combination of exercise and diet reduces EAT.[48] The exercises used in the studies included in the meta-analysis were aerobic exercise and/or resistance circuit training, and the exercise frequency was 2–3 times a week. EAT volume or thickness was quantified by CT, MRI, or echocardiography. Although exercise significantly reduced EAT and waist circumference, it did not affect BMI, body weight, or high-density lipoprotein.[48] Exercise significantly increased peak oxygen consumption.[48] Because that meta-analysis had some limitations, such as a high risk of bias due to insufficient blinding of the original studies and a small number of subjects in each study,[48] newer studies with better designs and methods are needed to improve the quality of the evidence.

Sodium-Glucose Cotransporter 2 (SGLT-2) Inhibitors

It is well known that SGLT-2 inhibitors, oral glucose-lowering agents, reduce body weight and visceral adiposity in patients with T2D. SGLT-2 inhibitors have been reported to reduce ectopic fat deposition, improving adipose tissue function and weight-related quality of life.[49] Recent studies have reported that SGLT-2 inhibitors reduce EAT. For example, we measured the EAT thickness of T2D patients by echocardiography before and after 3 and 6 months treatment with canagliflozin (**Figure 3**).[50] EAT thickness was significantly decreased, independent of decreases in

HbA1c, as early as after 3 months of treatment and continued to the 6-month time point.[50] There was a significant decrease in VAT volume at 3 months, but no further decrease after 6 months of therapy, as determined by a fat area analyzer using the bioelectrical impedance method.[50]

In another study, Fukuda et al used MRI to measure the EAT volume of non-obese T2D patients treated with ipragliflozin and found that EAT volume decreased significantly after 12 weeks of treatment.[51] The reduction in EAT was associated with a decline in BMI, and there was a significant decrease in VAT volume. There was no correlation between the reduction in VAT and the change in EAT volume.[51] Bouchi et al also used MRI to measure EAT volume in T2D patients with a BMI $\geq$25.0 kg/m^2 who were treated with luseogliflozin.[52] In that study, EAT volume decreased significantly after 12 weeks of treatment. The reduction in EAT volume was correlated with attenuation of systemic inflammation, as determined by C-reactive protein. However, luseogliflozin treatment did not significantly decrease VAT volume.[52]

Sato et al reported that in T2D patients with CAD, dapagliflozin significantly reduced EAT volume after 6 months, and the reduction in EAT volume was positively correlated with reductions in TNF-α concentrations.[53] VAT volume was not evaluated in that study.[53]

We have also investigated the effects of empagliflozin on PVAT and atherosclerosis in diabetic and hyperlipidemic animals and found that empagliflozin ameliorated endothelium-dependent vasodilation and inhibited atherosclerosis, suppressing inflammatory changes in periaortic adipose tissue.[54] Recently, a direct effect of an SGLT-2 inhibitor on EAT was reported.[55] In that study, EAT and subcutaneous adipose tissues obtained during cardiac surgery (n=49) were cultured. Dapagliflozin suppressed anaerobic glucose metabolism and reduced lactate release and acidosis in EAT without affecting lipid storage genes.[55] This effect was especially significant in EAT taken from CAD patients, independent of age and sex. Because high lactate levels are associated with cardiovascular outcomes, amelioration of glucose oxidation in the EAT by dapagliflozin may contribute to its protection against cardiovascular events.[55]

Together, these results suggest that SGLT-2 inhibitors reduce EAT volume with a suppression of inflammatory changes. Decreasing the EAT burden may contribute to the mechanism by which SGLT-2 inhibitors reduce cardiovascular events in large randomized clinical trials.[56,57]

Glucagon-Like Peptide-1 (GLP-1) Receptor Agonists

Recently, the efficacy and safety of GLP-1 receptor agonists have been reported.[58] Liraglutide was reported to decrease EAT volume in T2D patients.[59,60] Conversely, double-blinded placebo-controlled studies have reported that liraglutide does not reduce EAT volume,[61,62] although VAT volume was reduced by liraglutide in South Asian patients with T2D.[61] Because GLP-1 receptor agonists are reported to reduce cardiovascular events in T2D patients at high cardiovascular risk,[63,64] it is hoped that future studies will be able to demonstrate that GLP-1 receptor agonists can reduce EAT volume, with improvements in the inflammatory status, in appropriate patients when administered during an appropriate period.

Conclusions

Accumulating evidence suggests that EAT volume would be valuable in predicting the presence and prognosis of CAD, independent of conventional risk factors. New automated measurement methods with machine learning have been developed. Moreover, new imaging techniques have been reported to estimate the inflammatory status of EAT. Some treatments have been reported to reduce EAT volume and improve its quality. The quantity and quality of EAT may become a new risk factor for CAD and a biomarker for treatment.

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