

SPECIAL REVIEW ARTICLE

Possible Roles of Epicardial Adipose Tissue in the Pathogenesis of Coronary Atherosclerosis

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Abstract

Accumulating evidence revealed that adipose tissues secrete pro-inflammatory and anti-inflammatory humoral factors, called as adipocytokines. Most of the arteries are surrounded by perivascular adipose tissue (PVAT), which influences adjacent artery by secreting adipocytokines. PVATs are supposed to be athero-protective under healthy conditions, whereas PVATs are athero-promoting in obesity. Recent clinical studies suggested that coronary atherosclerosis is associated with increased volume of epicardial adipose tissue (EAT), PVAT of coronary artery. It was suggested that enhanced inflammation in EAT is also associated with vasospastic angina. In this review article, we will summarize recent findings about potential roles of EAT in the pathogenesis of coronary atherosclerosis.

Keywords: Adipocytokine, Adipose tissue, Atherosclerosis

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It is well known that the main functions of white adipose tissue are heat insulation, mechanical cushion and energy storage. Recently, adipose tissue is considered as an endocrine organ which secretes various adipocytokines. Adipocytokines regulate lipid metabolism, vascular homeostasis and inflammation. Most of the arteries are surrounded by perivascular adipose tissue (PVAT). PVAT has been considered as a simple supportive tissue of arteries. However, recent studies suggested that PVAT secretes adipocytokines which regulate vascular tone and inflammation and affect vascular function and atherosclerosis. Analyses of human epicardial adipose tissue (EAT), PVAT around the coronary artery, revealed that coronary artery disease (CAD) is associated with inflammatory EAT. In this review, we would like to summarize recent findings about the possible roles of EAT in the pathogenesis of atherosclerosis.

Perivascular adipose tissue regulates vascular responsiveness

Most of the arteries are surrounded by PVAT. However, there is a difference according to the parts of the arterial tree.

Aorta has abundant PVAT (1), while PVAT is absent around cerebral arteries and microvessels. There is no distinct border between PVAT and arterial adventitia. PVAT has been considered as a supportive tissue of vasculature. In 1991, it was demonstrated that removal of PVAT significantly reduced vascular responsiveness to contractile stimuli using a rat aortic ring (2). This study demonstrated a potential role for PVAT as a neurohumoral regulator of vascular responsiveness (2). Adipose tissue secretes so-called “adipocytokines”, including inflammatory and anti-inflammatory cytokines (3). It was reported that PVAT of human coronary arteries expresses inflammatory cytokines and chemokines (4, 5). PVAT also secretes reactive oxygen species (ROS), nitric oxide (NO), angiotensin II, and free fatty acid (FFA) that potentially influence vascular homeostasis (1). Adipocytokines secreted from PVAT appear to have access to the adjacent arterial wall directly or via vasa vasorum (VV) (6, 7) (Fig. 1).

Inflammation of perivascular adipose tissue promotes vascular lesion formation

We studied association between inflammation of PVAT and

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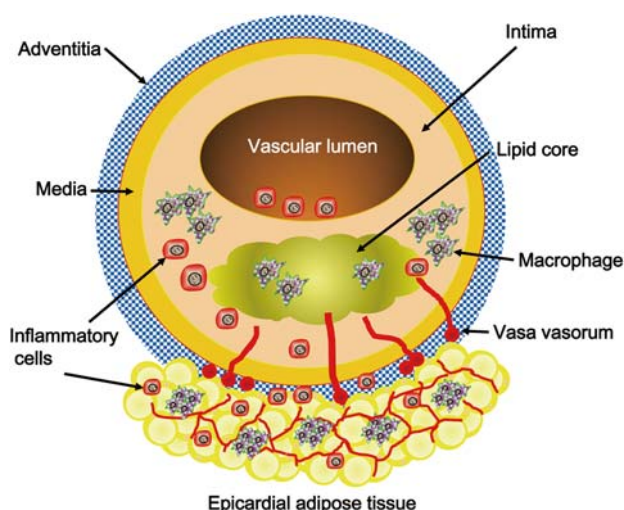


Fig. 1 Schematic illustration of coronary atherosclerosis plaque and epicardial adipose tissue (EAT). At the site of atherosclerotic lesions, EAT shows inflammatory phenotype with abundant infiltrations of macrophages and other inflammatory cells. Inflammatory EAT secretes various inflammatory adipocytokines to the adjacent coronary atherosclerotic lesion, leading to lesion development and destabilization. The secreted adipocytokines access to the adjacent artery wall directly or via vasa vasorum.

vascular lesion formation using animal models (8). First, we evaluated whether obesity leads to PVAT inflammation. Mice were fed on either a standard chow or a high-fat high-sucrose (HF/HS) diet. The HF/HS diet increased the body weight. In PVAT of the femoral arteries, the number of accumulated macrophages increased. Expression of adiponectin was down-regulated, while expression of inflammatory cytokines such as monocyte chemoattractant protein-1 (MCP-1), $\text{TNF-}\alpha$, and interleukin (IL)-6 was up-regulated in PVAT of mice fed on HF/HS diet. Next, endothelial denudation and over-dilatation were performed by inserting a wire into a femoral artery in the standard diet fed and the HF/HS diet fed mice. This injury model causes neointimal formation that mimics restenosis after human coronary angioplasty (9). The neointima formation in the HF/HS mice was exaggerated compared with that in the standard chow mice (Fig. 2). Replacement of PVAT with the subcutaneous fat from the mice fed on standard diet markedly attenuated the neointimal formation. Athero-protective effect was not observed when the subcutaneous fat from HF/HS mice or visceral fat was transplanted. These results indicated that the changes in adipocytokine expression in PVAT by HF/HS feeding influence pathological vascular remodeling in response to mechanical injury (8).

Next, we evaluated whether mechanical vascular injury affects the phenotype of PVAT (10). After the insertion of a wire into the femoral arteries of wild-type mice, the expression of inflammatory cytokines such as MCP-1, $\text{TNF-}\alpha$, IL-6 and plasminogen activator inhibitor-1 (PAI-1) increased in PVAT, while the expression of adiponectin decreased. Upregulation of proinflammatory cytokines was remarkably attenuated in

PVAT of $\text{TNF-}\alpha$ -deficient mice compared with that of wild-type mice after the femoral wire injury. It was suggested that $\text{TNF-}\alpha$ may play a pivotal role in transmitting endovascular injury to adipocytokine changes in PVAT (10).

Perivascular adipose tissue in coronary artery disease

Accumulating evidence suggests that EAT, PVAT of coronary artery, secretes cytokines to the adjacent coronary artery wall (6). For example, it was reported that EAT abundantly expressed IL-1 β , IL-6, $\text{TNF-}\alpha$ and MCP-1 compared with subcutaneous adipose tissue in patients undergoing coronary artery bypass graft (CABG) surgery (4). The expression of adiponectin mRNA was significantly lower in EAT than in gluteal and abdominal adipose tissue depots (11). We also analyzed EAT obtained during cardiac surgery (12, 13). We collected EAT and subcutaneous adipose tissue (SCAT) from 38 CAD patients undergoing CABG and 40 non-CAD patients undergoing valvular surgery (13). Expression of IL-6 and $\text{TNF-}\alpha$ in EAT was higher in the CAD group than in the non-CAD group. There was no significant difference between the CAD and the non-CAD groups in the expression of adipocytokines in SCAT. Infiltration of macrophages in EAT was significantly higher in the CAD group than in the non-CAD group. The number of M1 macrophages relatively increased with relative decrease in M2 macrophages in the CAD group. The ratio of M1/M2 macrophages was correlated positively with the severity of CAD as determined by Gensini score (14) (Fig. 3), indicating that macrophage polarity in EAT has significant role in the pathogenesis of atherosclerosis.

Evaluation of epicardial adipose tissue volume

EAT volume has been quantified by coronary artery computed tomography (CT), echocardiography and magnetic resonance imaging (MRI). Recently, many groups demonstrated that increased EAT volume is associated with CAD (15, 16). However, there might be a confusion in definition of fat depots around the heart (17). EAT, located inside the parietal pericardium, have a direct contact with coronary artery, whereas adipose tissue located outside the parietal pericardium is called as paracardial adipose tissue (PAT). PAT is also called as thoracic or intrathoracic adipose tissue. In some studies, PAT was described as “pericardial adipose tissue”, whereas EAT or EAT together with PAT were described as “pericardial adipose tissue” in other studies (17). EAT and PAT have distinct characteristics because EAT shares coronary circulation with cardiac myocardium, while PAT is perfused by non-coronary source. We would like to define “epicardial adipose tissue” plus paracardial adipose tissue as “pericardial adipose tissue”.

To evaluate EAT accumulation, different groups use EAT

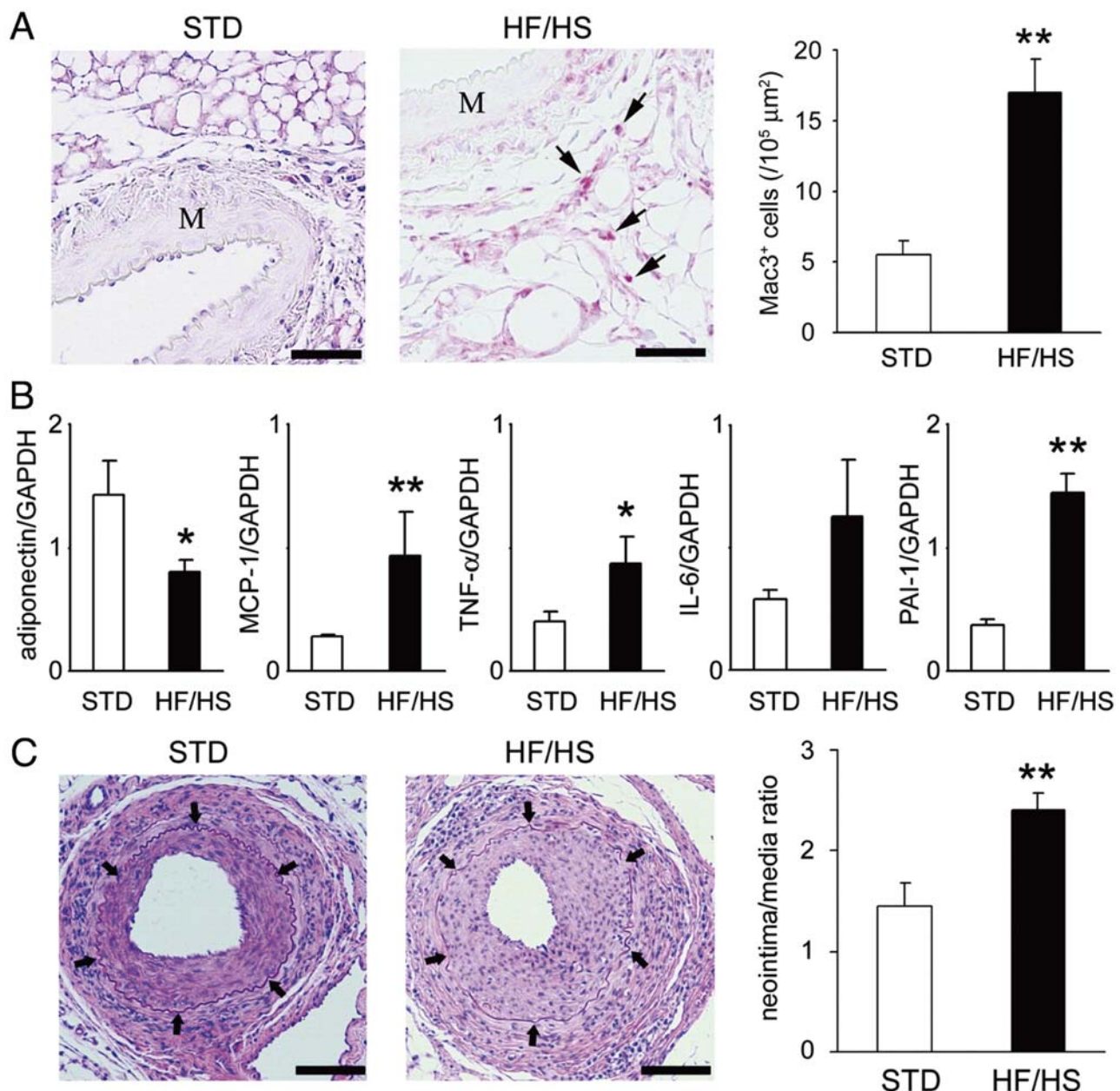


Fig. 2 Obesity-induced inflammatory changes in periaortic fat and enhanced neointimal hyperplasia. **A**, Obesity-induced accumulation of inflammatory cells in periaortic fat tissue (PVAT). Immunohistochemical analysis showed accumulation of Mac3-positive macrophages (arrows) within periaortic fat in obese mice. Scale bar: 50 μm. Results are expressed as mean ± SEM. **P<0.01. M indicates media of femoral artery. **B**, Expression of mRNA in periaortic fat around femoral artery from STD (standard diet) (n=6) and HF/HS (high fat/high sucrose diet) WT C57BL/6 mice. Expression level was assessed by real-time PCR normalized to each GAPDH level. Results are expressed as mean ± SEM. *P<0.05, **P<0.01. **C**, Hematoxylin/eosin-stained sections of femoral arteries from mice fed STD or HF/HS diet 4 weeks after endovascular injury. Arrows indicate internal elastic lamina. Scale bar: 100 μm. Morphometric analysis of injured femoral arteries in lean (n=7) and obese (n=6) mice 4 weeks after wire-induced injury. Results are expressed as means ± SEM. **P<0.01. All figures are adopted from reference (8) with permission.

volume (15, 18) or EAT volume index, which is EAT volume divided by body surface area (BSA) (16). We found that the EAT volume was higher in men than in women, whereas the EAT volume/height and EAT volume index were comparable (16). Therefore, EAT volume index might be a preferable parameter when the study subject includes both men and women.

We investigated the impact of EAT volume index on CAD (16). EAT volume index was evaluated in 90 consecutive patients who underwent CT coronary angiography (age, 63 ± 12 years; 22 CAD men, 25 non-CAD men, 16 CAD women, 27 non-CAD women). EAT volume was measured as the sum of cross-sectional fat area on CT images, from the lower surface of the left pulmonary artery origin to the apex.

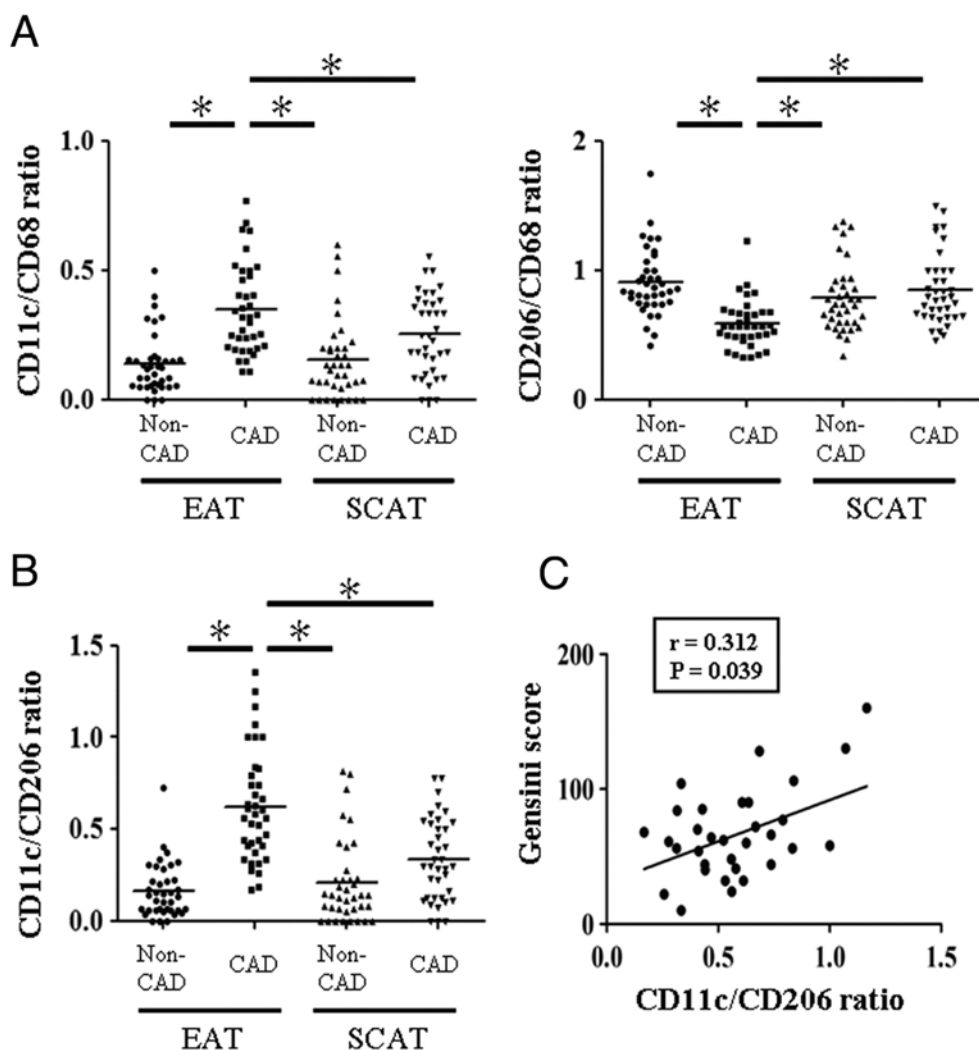


Fig. 3 M1/M2 macrophage polarization in EAT and SCAT.

Each point represents the ratio of (A) CD11c- and CD206-positive cells to CD68-positive cells and (B) CD11c-positive cells to CD206-positive cells. Bar indicates mean. * $P < 0.05$. (C) Correlation of Gensini score with ratio of CD11c/CD206-positive cells in EAT in CAD group. SCAT, subcutaneous adipose tissue. All figures are adopted from the reference (13) with permission.

Multivariate analysis showed that EAT volume index was the single predictor for CAD (>50% coronary artery narrowing) in men, whereas BMI, age, presence of hypertension, diabetes mellitus, and hyperlipidemia were not associated with the presence of CAD. On the other hand, the EAT volume indexes did not differ significantly between CAD and non-CAD groups in women.

We also evaluated the relation between the EAT volume index and the characteristics of EAT (19). We collected EAT and SCAT from 50 CAD patients and 50 non-CAD patients who underwent elective cardiac surgery. EAT volume index had positive correlation with the number of CD68, CD11c positive M1 macrophages, and the expression of inflammatory cytokines such as IL-1 β . EAT volume index was negatively correlated with adiponectin expression in EAT (19). A multivariate analysis model including CD68 positive cells and IL-1 β expression and adiponectin expression in EAT strongly

predicted CAD. These results suggested that increased EAT volume with increased infiltration of macrophages and up-regulation of inflammatory adipocytokines is associated with CAD.

Evaluation of EAT thickness by echocardiography

Another method to quantify EAT is to measure EAT thickness by echocardiography. Recently, we developed a new method to evaluate EAT thickness by echocardiography using a high frequency linear probe (20). We measured EAT thickness at anterior interventricular groove (EAT-AIG) and at anterior right ventricle (EAT-RV) of 311 patients who underwent coronary angiography (166 CAD; 145 non-CAD). 71 patients underwent both CT coronary angiography and echocardiography. It was validated that EAT-AIG thickness had a strong correlation with EAT volume evaluated by CT coronary angiography. Both EAT-AIG and EAT-RV of CAD

patients were thicker than those of non-CAD patients. EAT-AIG thickness was more strongly associated with CAD as determined by the receiver operating characteristics curve analysis. It was indicated that CAD could be predicted with high sensitivity and specificity by evaluating EAT thickness (20).

Other imaging modalities to evaluate EAT volume

EAT volume also could be measured by MRI. Gohbara et al. measured EAT volume of the patients with ST-segment elevation myocardial infarction (STEMI) by MRI. In contrast to the previous studies that suggested the relation between EAT with CAD, the lower EAT volume was associated with less myocardial salvage and larger infarct size. In this study, the adiponectin level was negatively correlated with the EAT volume. The authors concluded that the decreased adiponectin level in the patients with decreased EAT led to more myocardial damage by SEMI (21).

Recently, Ohyama et al. reported that vasospastic angina (VSA) is associated with inflammation in coronary adventitia and EAT, using CT coronary angiography and electrocardiogram (ECG)-gated ^{18}F -fluorodeoxyglucose (^{18}F -FDG) positron emission tomography/CT (PET/CT) (22). After excluding patients with $\geq 75\%$ organic stenosis in left anterior descending coronary artery (LAD), the patients with suspected VSA were divided into VSA group ($n=27$) and non-VSA group ($n=13$) by spasm provocation test with intracoronary acetylcholine infusion. ECG-gated ^{18}F -FDG PET/CT was performed to measure coronary perivascular FDG uptake. Optical coherence tomography was also performed to evaluate VV of LAD. Coronary PVAT volume index was measured by CT coronary angiography at the spastic LAD. ^{18}F -FDG PET/CT images showed that coronary perivascular FDG uptake was significantly increased at the spastic LAD in the VSA group compared with that of non-VSA group. Coronary perivascular target-to-background ratio had a significant positive correlation with the extent of coronary PVAT volume index in the VSA group, but not in the non-VSA group. Optical coherence tomography (OCT) examination showed that adventitial VV area density per a cross-sectional OCT image at the spastic LAD was markedly greater in the VSA group than in the non-VSA group. After 23 months follow-up with medical treatment, coronary perivascular FDG uptake was significantly decreased in the VSA patients. Rho-kinase activity in circulating leukocytes increased in the VAS patients and substantially decreased after medical treatment. ^{18}F -FDG PET/CT reflects tissue inflammation because of the glucose metabolism is enhanced in inflamed tissue. Therefore, this study clarified the VSA is associated with EAT inflammation and VV formation.

Possible role EAT in the pathogenesis of atrial fibrillation

Recent studies suggested that EAT might be associated with atrial fibrillation (AF) (23). In Framingham heart cohort, peri-atrial EAT volume was measured by CT in 3217 subjects. It was suggested that EAT volume was an independent risk factor of AF after adjusting other risk factors such as hypertension, PR interval and body mass index (BMI) (24). Another study demonstrated that peri-atrial EAT volume excellently predicted the development of new-onset AF in patients with CAD, independent of enlargement of the left atrium (25). It is speculated that inflammatory cytokines such as IL-6, IL-8, IL-1 β and TNF- α secreted from peri-atrial EAT promote fibrotic remodeling of atrial myocardium, leading to AF (26).

Conclusions

EAT has been considered to have impacts on the function and lesion formation of adjacent coronary arteries by secreting inflammatory adipocytokines. It was indicated that the increased accumulation of EAT is associated with EAT inflammation and CAD. It remains to be clarified whether EAT could be reduced by life-style modification and/or medical treatment, leading to prevention of CAD. More detailed analyses are needed to clarify the roles of EAT in pathogenesis of CAD.

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Conflicts of interest

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