Epicardial and Perivascular Adipose Tissues and Their Influence on Cardiovascular Disease: Basic Mechanisms and Clinical Associations

Timothy P. Fitzgibbons, MD, PhD; Michael P. Czech, PhD

It is well established that the cardiovascular (CV) risk of obesity is more strongly associated with visceral rather than subcutaneous adiposity.[1–3] Anthropometric variables that account for visceral adiposity, such as body mass index (BMI) and waist circumference (WC), have limited sensitivity and specificity. Furthermore, there is increasing recognition of "normal weight obese" persons (ie, those with increased visceral adipose but normal WC) who are prone to the same risk of the metabolic syndrome.[4] These patients are detected only through abdominal computed tomography (CT) or magnetic resonance imaging (MRI). Rapid advancements in non-invasive cardiac imaging techniques have fostered interest in the imaging of perivascular and epicardial fat as proxy measures of visceral adiposity and, hence, more sensitive and specific indicators of cardiometabolic risk.[5,6] The idea that these fat depots may not only be representative of abdominal visceral adipose tissue (VAT) but perhaps independently causal of CV disease (CVD) is an attractive one that is rapidly gaining traction. The potential roles of perivascular and epicardial fat in obesity-associated CVD are best understood in the context of the pathophysiology of obesity-induced insulin resistance.

Basic Mechanisms

"Immunometabolism": Inflammation of VAT and the Development of Insulin Resistance

The idea that obesity is associated with a chronic inflammatory response in visceral fat dates to seminal articles published almost 20 years ago.[7–9] These studies showed that tumor necrosis factor (TNF)-α levels were increased in the adipose tissue of obese humans and mice and demonstrated infiltration of macrophages into the VAT of obese mice.[7–9] Chronic caloric excess in the face of reduced energy expenditure causes increased visceral fat mass, due to hypertrophy of individual adipocytes and hyperplasia of adipocyte precursors. Increased adipocyte size results in the release of chemotactic factors such as monocyte chemoattractant protein-1 (MCP-1), which initiate the migration of monocytes into VAT and promote their differentiation into macrophages.[10] The trigger for the initiation of blood monocyte chemotaxis into VAT is multifactorial; adipocyte apoptosis, increased lipolysis and local free fatty acids, reactive oxygen species (ROS), and/or tissue hypoxia may also play a role.[11] The differentiation of infiltrated monocytes into proinflammatory macrophages (M1 or "classically activated") results in the local production of cytokines such as interleukin (IL)-1β, TNF-α, and IL-6. TNF-α production by macrophages directly inhibits insulin signaling in adipocytes, causing decreased glucose transport, decreased free fatty acid uptake and reesterfication, and increased lipolysis.[12] Based on these considerations, the resultant failure of VAT to store triglyceride could result in the ectopic accumulation of toxic fatty acids species (eg, diacylglycerol, ceramide) in skeletal muscle, liver, pancreas, and myocardium, which contribute to end-organ and ultimately systemic insulin resistance.[12] In particular, the proximity of inflamed VAT to the portal circulation allows released fatty acids and cytokines to directly affect the liver and are thought to contribute to hepatic insulin resistance and hepatic steatosis.[13] Interestingly, some have suggested that epicardial adipose tissue (EAT) may play a similarly important role in myocardial steatosis, due to its anatomic proximity and absence of a dividing fascial plane.[14]

Aspects of this long-standing paradigm, which is the foundation for the burgeoning field of "immunometabolism," have recently been challenged. First, increased plasma concentrations of free fatty acids do not always result in insulin resistance.[15] Second, in some instances, for example negative caloric balance (ie, fasting), macrophage infiltration

into VAT is protective.[16] Finally, not only the monocyte/ macrophage, but virtually every type of immune cell, has been implicated in the orchestration of a broad inflammatory response in VAT in response to high-fat feeding.[17–21] However, that activated peripheral blood monocytes play an essential and perhaps primary role is evidenced by the fact that specific depletion of Cd11c$^+$ macrophages in a diet-induced obesity model ameliorates insulin resistance.[22]

Beneficial Effects of Perivascular Adipose Tissue and EAT

It should be emphasized that perivascular and epicardial fat are normally present in humans and other mammals. However, in obesity, the size of these fat depots is increased, commensurate with increases in visceral fat. Therefore, this is not "ectopic fat" per se but rather hypertrophy of a normal anatomic structure. EAT predominantly functions as perivascular adipose tissue (PVAT) for the coronary arteries, following their course, and being concentrated in the acute marginal, atrio-ventricular, and interventricular sulci[23] (Figure 1). With the exception of the lateral wall of the right and the anterior wall of the left, the walls of the ventricles are free of epicardial fat.[23] EAT displays high rates of both lipogenesis and lipolysis and has been proposed to serve as local fat storage depot, storing excess free fatty acids as triglyceride at times of excess and releasing them to the heart for substrate in times of metabolic stress.[34] In addition to surrounding the coronary arteries, PVAT surrounds large (aorta), medium-size (mesenteric), and small arteries (gluteal), and its function likely differs in each of these anatomic contexts (Figure 1). In this review, we use the term "PVAT" broadly, understanding that different functions may be common to different vascular beds.

In lean humans and rodents, PVAT has been shown to express and secrete many putatively beneficial adipokines, of which adiponectin (ADIPOQ) appears to be the most prominent[32,35–38] (Table 1). In lean humans, PVAT-derived ADIPOQ has vasodilatory properties on small arteries from gluteal fat.[32] This anticontractile function is lost in obesity, due to decreased PVAT ADIPOQ and increased TNF-α concentrations.[32] After gastric bypass and a mean reduction in BMI from 51.5 to 37.9 kg/m^2, the anticontractile effect of PVAT was restored, in conjunction with an increase in PVAT ADIPOQ concentrations.[35] In both instances, this anticontractile effect was abrogated by preincubation with anti-AdipoR1 antibodies or removal of PVAT.[32,35] ADIPOQ also modulates endothelium-*dependent* vasodilation. A recent study using PVAT from human saphenous vein grafts and internal mammary arteries showed that PVAT-derived ADIPOQ stimulates local endothelial nitric oxide synthetase (eNOS/NOS3) function via 2
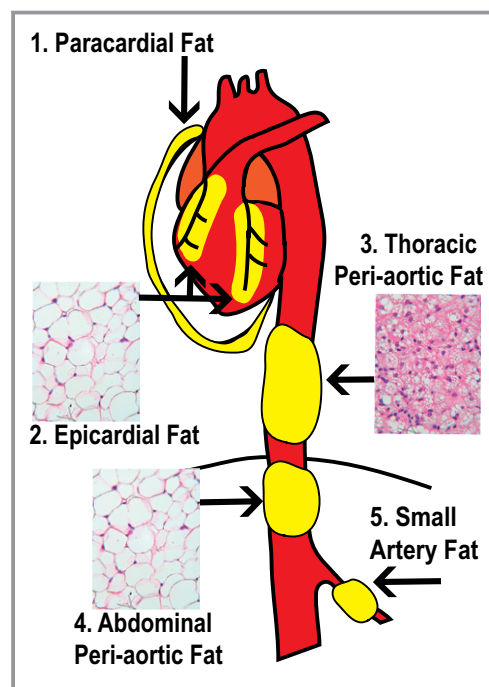

Figure 1. Anatomy and nomenclature of commonly studied perivascular adipose depots. (1) Paracardial adipose tissue (PAT) is the fat that surrounds the parietal pericardium; it is also referred to as "mediastinal fat" or "thoracic" fat. Recent human data suggest that this fat may be "beige" in morphology—that is, having features of both white and brown adipose tissue.[24] Measurement of paracardial fat volume is often used in imaging studies and may or may not be specifically differentiated from the underlying epicardial fat. (2) Epicardial adipose tissue (EAT) is encased by the visceral pericardium, lying directly adjacent to the myocardium and surrounding the coronary arteries. Here, it is shown surrounding the right coronary artery (RCA) and left anterior descending coronary artery (LAD). Human EAT is morphologically similar to white adipose tissue.[25] *Peri*cardial fat has been defined as the combination of *para*cardial and *epi*cardial fat.[26] (3) Thoracic periaortic fat surrounds the thoracic aorta in humans and rodents. In rodents, it is morphologically and functionally identical to brown adipose tissue; whether this is the case in humans remains unknown.[27–30] (4) Abdominal periaortic fat surrounds the abdominal aorta and has features of white adipose tissue in rodents and humans.[29,31] (5) Small artery fat, or that surrounding the mesenteric arteries and smaller arteries, usually has features of white adipose. Fat surrounding small arteries (ie, resistance vessels) may play a role in regulating vascular tone and flow of metabolites/nutrients, as originally proposed by Yudkin.[32,33]

mechanisms: stimulation of AKT-dependent phosphorylation and increased tetrahydrobiopterin (BH$_4$) synthesis[38] (Figure 2).

ADIPOQ also has potent anti-inflammatory effects in multiple cell types.[44] For example, it suppresses adipocyte production of TNF-α and C-reactive protein.[44] Adipoq$^{-/-}$ mice have increased expression of endothelial cell adhesion molecules and greater inflammation in mesenteric fat.[45] ADIPOQ suppresses activation of nuclear factor κ-light-chain-enhancer of activated B cells in endothelial cells via both

Table 1. Vasculoprotective Factors Released From EAT and/or PVAT in Human and Animal Studies

Factor	Effects
Adiponectin	• Endothelium-independent vasodilation[32,35] • Inhibition of vascular smooth muscle proliferation in vivo and in vitro via an AMPK-dependent pathway[36] • Prevents monocyte adhesion to HAECs[37] • Activation of local eNOS function by stimulatory phosphorylation and increased BH_4 production[38]
Leptin	• Endothelium-dependent dilation of conduit arteries[39]
Omentin-1	• EAT and plasma levels of omentin are reduced in diabetic patients[40] • Recombinant omentin prevented the inhibitory effects of CM-EAT-DM on contraction of ARVC and insulin-stimulated Akt-Ser473 phosphorylation[40]
Nitric oxide	• Endothelium-dependent vasodilation[32]
PAME	• Vasodilation via direct stimulation of VSMC potassium channels[41]
PGI_2	• PVAT-derived prostacylin may inhibit endothelial dysfunction by impairing acetylcholine-induced vasoconstriction[30]

EAT indicates epicardial adipose tissue; PVAT, perivascular adipose tissue; AMPK, adenosine monophosphate–activated protein kinase; HAEC, human aortic endothelial cell; eNOS, endothelial nitric oxide synthetase; BH_4, tetrahydrobiopterin; CM-EAT-DM, conditioned media from epicardial adipose of diabetic patients; ARVC, adult rat ventricular cardiomyocyte; PAME, palmitic acid methyl ester; VSMC, vascular smooth muscle cell; PGI_2, prostacyclin.

cyclic AMP–protein kinase A and AMP-regulated protein kinase pathways.[45] Finally, ADIPOQ suppresses IL-6, TNF-α, and scavenger receptor A expression in macrophages; while increasing expression of the anti-inflammatory cytokine IL-10.[44] Not only do the specific anti-inflammatory effects of ADIPOQ vary based on the cellular context, but they are also dependent on the concentration and molecular weight of the circulating hexamer (ie, low or high molecular weight).[45]

Additional beneficial paracrine effects of PVAT-derived ADIPOQ in mice have been described.[36] In mouse femoral arteries, PVAT-derived ADIPOQ prevents neointimal hyperplasia in response to wire vessel injury.[36] This effect was shown to be due to AMP-regulated protein kinase–dependent inhibition of platelet-derived growth factor (PDGF)-stimulated smooth muscle cell growth (Figure 2). Thus, in both lean mice and humans, PVAT secretes ADIPOQ, which has at least 3 beneficial effects on the underlying vasculature: stimulation of endothelium-dependent and -independent vasodilation, inhibition of inflammation, and inhibition of growth factor–stimulated vascular smooth muscle cell (VSMC) growth.[32,38]

Pathological Effects of Dysregulated Perivascular Adipocytes

Despite these putative beneficial effects, analogous to VAT, EAT is subject to the maladaptive adipocyte biology of obesity, which is characterized by hypertrophy, failure to store triglyceride, increased lipolysis, and inflammation. In this setting, the beneficial paracrine effects of EAT (ie, ADIPOQ release, fatty acid uptake) are abrogated, and a causative role in local inflammation and CV pathophysiology may be assumed (Figure 2). There appears to be mechanisms in the PVAT of lean mice that restrain inflammation, such as the mammalian target of rapamycin complex 2 (mTORC2)[42] (Figure 2). Not only does mTORC2 suppress inflammatory cytokine expression, but it also appears to suppress expression of inducible nitric oxide synthetase (iNOS/NOS2) by the adipocyte itself.[42] Downregulation of mTORC2 signaling causes induction of adipocyte iNOS, leading to unregulated nitric oxide production and generation of ROS such as peroxynitrite ($ONOO^-$), which directly cause vasoconstriction of vascular smooth muscle cells (Figure 2). This represents a provocative mechanism via which metabolic stress in adipocytes may simultaneously initiate inflammation and vasoconstriction.

Not only the degree but also the nature of local inflammatory responses influence the biology of EAT. In patients with advanced coronary artery disease (CAD), there is increased staining for $CD11c^+$ cells in EAT, a marker of inflammatory (M1 or "classically activated") macrophages.[46] In contrast, in patients without CAD, there is increased $CD206^+$ staining, which is a marker of anti-inflammatory macrophage (M2 or "alternatively activated") polarity.[46] The transition of resident macrophages from a resting anti-inflammatory (M2) state to an activated (M1) state may be a manifestation of lipotoxicity[47]; how this might relate to the development plaque in adjacent coronary arteries is unknown.

In parallel to this inflammatory state in EAT, beneficial adipokine production is decreased in obesity. For example, ADIPOQ secretion from EAT is suppressed in patients with obesity and/or CAD.[37,48] Interestingly, expression of ADIPOQ in EAT may or may not correlate with plasma concentrations, which are presumably derived from subcutaneous adipose tissue (SAT) and most often decreased in obesity.[38]

The concept that adventital inflammation might stimulate disease of the underlying vessel stems from initial studies of human abdominal aortic PVAT and EAT.[31,49] PVAT from atherosclerotic abdominal aortas was found to secrete MCP-1 and IL-8 in concentrations equivalent to paired subcutaneous fat[31] (Table 2). The functional significance of these factors was suggested by the ability of both subcutaneous fat and PVAT to stimulate leukocyte chemotaxis in transwell assays and the observation that $CD68^+$ and $CD3^+$ cells were present in PVAT.[31] EAT from patients with CAD was found to have higher mRNA and protein levels of inflammatory cytokines (IL-1β, IL-6, MCP-1, and TNF-α) than paired subcutaneous fat. Expression of these factors was associated with dense inflammatory infiltrates of macrophages,
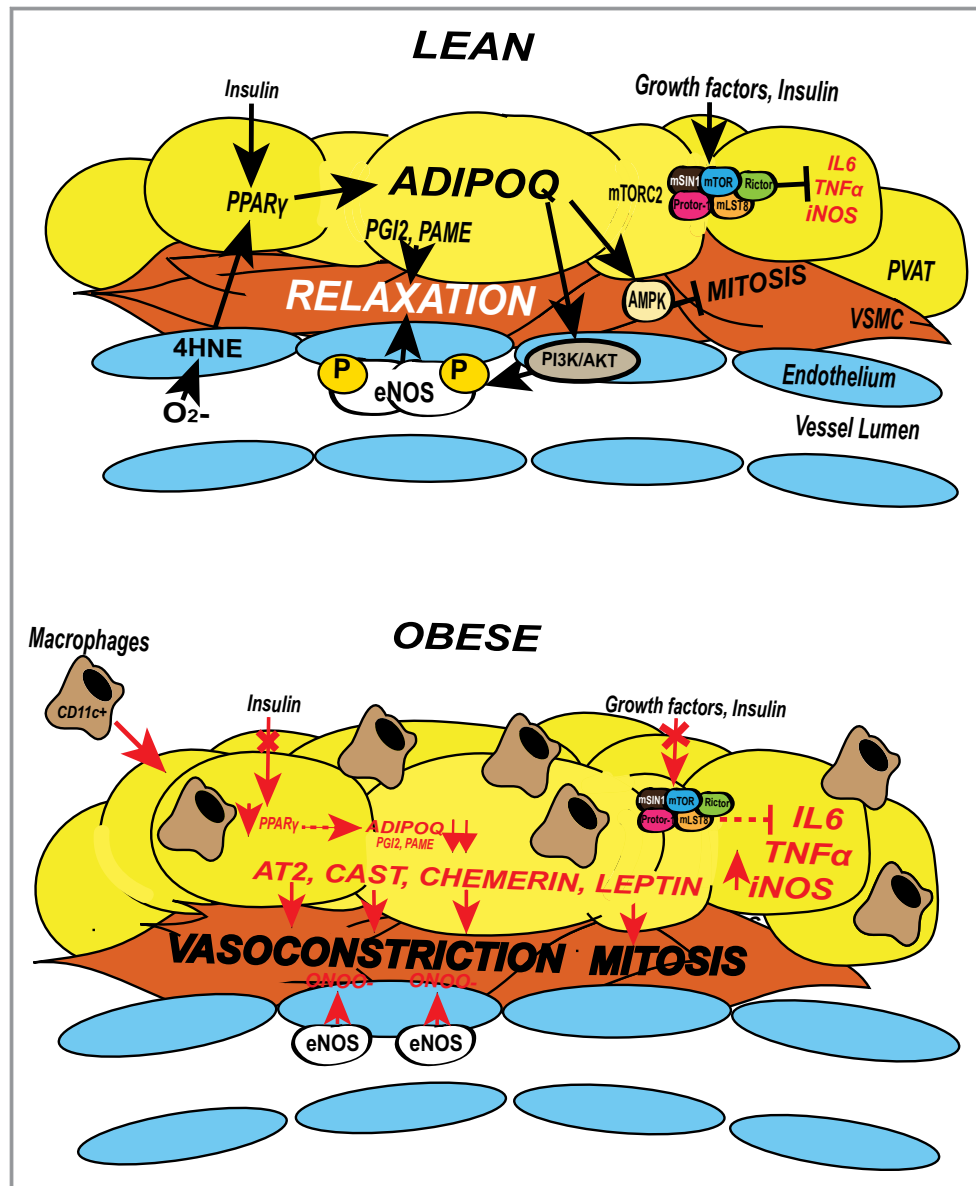
Figure 2. Signaling pathways that mediate the paracrine effects of PVAT. Adiponectin (ADIPOQ) has been shown to mediate many of the beneficial effects of PVAT. ADIPOQ is more highly expressed in lean conditions (top) than in obese conditions (bottom). ADIPOQ causes arterial vasodilation by promoting local eNOS activity in 2 ways: stimulation of AKT-dependent phosphorylation and subsequent increased eNOS coupling, and by increasing BH$_4$ cofactor availability.[38] ROS byproducts generated by dysfunctional endothelium (4HNE) feedback to activate PPARγ in adjacent PVAT, thereby stimulating transcription of ADIPOQ and other downstream adipogenic genes. ADIPOQ also promotes endothelium-*independent* vasodilation by activation of VSMC potassium channels (not shown). ADIPOQ released by healthy PVAT prevents neointimal hyperplasia by suppressing mitosis of VSMCs in an AMPK-dependent mechanism[36] (top). Lipids such as palmitic acid methyl ester (PAME) and prostacyclin (PGI$_2$) have also been shown to stimulate endothelium-independent vasodilation via direct activation of VSMC potassium channels and PGI$_2$ receptor activation (top).[30,41] Finally, in PVAT from lean mice, unknown growth factor signals converge on mTORC2, resulting in Akt activation and inhibition of inflammatory cytokine production by adipocytes; loss of mTORC2 signaling in Rictor-deficient mice results in increased inflammation and increased vasoconstriction of underlying VSMC (top).[42] In obesity, these pathways may be compromised, or new pathological mechanisms may emerge (bottom). Obesity stimulates inflammation and macrophage infiltration, which increases local cytokine and ROS production (bottom). The resultant impairment of insulin signaling contributes to a reduction in beneficial adipokine expression (ADIPOQ, PAME, PGI$_2$), uncoupling of eNOS, and increased expression of pathological vasoconstricting factors (angiotensin 2 [AT2], chemerin, and calpastatin).[43] PVAT from obese patients may also release factors that stimulate mitosis (eg, leptin, PDGF) of VSMCs by overwhelming local beneficial adipokine effects.[36,41] AMPK indicates adenosine monophosphate kinase; BH$_4$, tetrahydrobiopterin; eNOS, endothelial nitric oxide synthetase; 4HNE, 4-hydroxynonenal; IL-6, interleukin 6; iNOS, inducible nitric oxide synthetase; mLST8, MTOR associated protein, LST8; mTORC2, mammalian target of rapamycin complex 2; ONOO$^-$, peroxynitrite; PDGF, platelet-derived growth factor; PI3K/AKT, Phosphoinositide 3-kinase; PPARγ, peroxisome proliferator–activated receptor gamma; PVAT, perivascular adipose tissue; ROS, reactive oxygen species; TNFα, tumor necrosis factor alpha; VSMC, vascular smooth muscle cell.

Table 2. Pathological Factors Released From EAT and/or PVAT in Human and Animal Studies

Factor	Effect
Activin A	• Increased fibrosis of rat atrial myocytes treated with conditioned media in vitro[50] • Cardiodepressant effect on ARVCs in vitro by reducing expression of SERCA2a[51]
Angiopoietin	• Cardiodepressant effect on ARVCs in vitro by reducing expression of SERCA2a[51]
Angptl-2	• Promotes adventitial inflammation in vivo[52]
Angiotensin II	• Increased vasoconstriction of aortic rings, blocked by incubation with ATIIR blocker[41]
Calpastatin/CAST	• Protein is a partial agonist for intracellular domains of $Ca_v1.2$ • Dose-dependently increases coronary arterial contractions like PVAT[43]
Chemerin/*RARRES2*	• May directly stimulate vasoconstriction by binding to ChemR23, which is found on VSMCs[53]
Complement component 3	• Stimulates differentiation and migration of adventitial myofibroblasts[54]
Leptin	• Local leptin levels may promote neointima formation indepedently of obesity or inflammation[55]
IL-6, MCP-1, PAI-1, GROα, sICAM-1, sIL-6R, RANTES	• Conditioned media from patients with CAD increased THP1 monocyte adhesion and migration in vitro[31,37]
Resistin	• Stimulates endothelial cell permeability in vitro[56]
Secretory type II phospholipase A2	• Promotes formation of inflammatory lipid mediators in EAT[57]
TNFα	• Loss of vasodilator effect of PVAT; likely due to downregulation of NOS by TNFα[32]
VEGF	• VEGF expression was increased in the VAT and EAT of diabetic patients and stimulated greater proliferation of VSMCs in vitro[58]
Visfatin	• Stimulation of vascular smooth muscle proliferation in vitro[59]

EAT indicates epicardial adipose tissue; PVAT, perivascular adipose tissue; ARVC, adult rat ventricular cardiomyocyte; SERCA2, sarcoplasmic reticulum Ca^{2+} ATPase; ATIIR, angiotensin II receptor; CAST, ; ChemR23, Chemerin receptor 23; VSMC, vascular smooth muscle cell; IL-6, interleukin 6; MCP-1, monocyte chemoattractant protein-1; PAI-1, plasminogen activator inhibitor-1; GROα, growth-regulated oncogene α; sICAM-1, soluble intercellular adhesion molecule 1; sIL-6R, soluble IL-6 receptor; RANTES, Regulated on Activation, Normal T cell Expressed and Secreted; CAD, coronary artery disease; THP1, Human acute monocytic leukemia cell line; TNFα, tumor necrosis factor α; NOS, nitric oxide synthase; VEGF, vascular endothelial growth factor; VAT, visceral adipose tissue.

T cells, and mast cells in EAT.[49] The authors concluded that EAT from patients with CAD is associated with increased inflammatory gene expression, which may affect the development or progression of atherosclerosis. Many subsequent studies have demonstrated increased expression of proinflammatory cytokines in EAT from patients with CAD.[56,60–62] However, because a normal control group was not present in most studies, the degree to which inflammation was causative or reactive to local atherosclerotic lesions remains unknown.[49]

Finally, it should be emphasized that PVAT is an intimate part of the adventitia that contains many different cell types (eg, adipocytes, endothelial cells, fibroblasts) with interrelated functions. Not only obesity, but other pathological conditions such as hypertension, or balloon inflation during percutaneous intervention, may initiate a response in PVAT. For example, among the most abundant proteins secreted by rodent PVAT is complement component 3 (C3).[54] C3 from PVAT–conditioned media stimulates adventitial fibroblast migration and differentiation via c-Jun N-terminal kinase activation.[54] This effect is increased in the deoxycorticosterone acetate–salt hypertensive rat and is thought to contribute to adventitial remodeling and increased vascular stiffness.

Brown Fat–Like Attributes in the Perivascular Niche

Adipose tissue in different anatomic locations, or even within the same depot, may differ with regard to its metabolic function. In general, adipose tissue can be thought of as belonging to 2 broad functional categories. White adipose tissue (WAT) consists of large unilocular adipocytes whose primary function is to store energy in the form of triglyceride. Brown adipose tissue (BAT) contains multilocular adipocytes with large numbers of mitochondria and is most commonly found in young mammals and rodents. Its primary function is to generate heat via uncoupled oxidative phosphorylation. A third type of adipocyte, termed the "brite" or "beige" adipocyte, is a brown adipocyte that arises within white adipose depots and also has thermogenic capacity.[63,64] There is great interest within the metabolic field in activating the formation of BAT to facilitate expenditure of energy, promote weight loss, and prevent obesity and diabetes. This interest has been sparked by recent data that suggest, contrary to prior thought, that BAT is present in adult humans and correlates with leanness, age, female sex, and insulin sensitivity.[65,66] These fascinating aspects of BAT are the topic of many recent excellent reviews.[63,67,68]

Interestingly, mRNA expression of uncoupling protein-1 (UCP-1) is high in EAT in comparison to other fat depots, leading some to speculate that it may function as BAT to generate heat and protect the myocardium from hypothermia.[69] UCP-1 is also increased at the protein level, and there is increased expression of genes specific for beige adipocytes.[25] Despite the presence of UCP-1 protein and beige cell gene expression, histological studies showed that EAT contained unilocular cells, consistent with purely white adipocytes[25] (Figure 1). Fat adjacent to the subclavian artery, however, did show morphological features consistent with a beige cell origin (ie, round nuclei, multilocular lipid droplets).[25] In short, there is no definitive evidence to date that brown fat exists in the perivascular niche in humans. This may be due to the fact that in most cases, sampling of epicardial and perivascular fat is done when humans are older or already have established vascular disease, two instances in which one might not expect to find BAT.

In contrast, there are abundant data in rodents that demonstrates bona fide brown adipose surrounding the thoracic aorta.[27–30] There is a dichotomy in the morphology of the aortic PVAT in rodents—that above the diaphragm being brown and that below being white (Figure 1). BAT, unlike WAT, tends to be resistant to high-fat diet–induced inflammation.[27] Therefore, the presence of brown PVAT may be protective, whereas WAT surrounding the abdominal aorta may lead to adventitial inflammation and promote abdominal aortic aneurysm formation in obese patients.[29]

A major limitation to this field is that most studies demonstrate association but not causality. There have been recent elegant attempts to address this problem using removal or transplantation of fat to the perivascular space.[36,55,70] These studies are prone to some methodological limitations. For example, only vessels that are easily accessed with surgical technique (ie, femoral, carotid) are available to study. Second, transplanted fat is usually VAT or SAT. The small amount of PVAT surrounding native rodent vessels is generally prohibitive to transplantation studies. Finally, the process of transplantation itself causes an inflammatory response in the transplanted fat pad that is artificial and unlikely to represent native physiology.[71] Nonetheless, it does seem to recapitulate the inflammatory response of VAT to a high-fat diet and is, importantly, absent in transplanted SAT.[71] Therefore, transplantation studies do offer important insight into the potential impact of PVAT on vascular physiology and disease.

In 2009, Takaoka et al[36] published the first of these studies using the femoral artery wire injury model. They established that normal PVAT has an important effect to prevent neointimal hyperplasia in response to vessel injury; femoral arteries stripped of PVAT had excessive neointimal hyperplasia.[36] Transplantation of normal SAT to the femoral

artery rescued this effect, whereas transplantation of VAT from high-fat diet–fed animals exaggerated it. The authors concluded that inhibition of neointimal hyperplasia was dependent on PVAT-derived ADIPOQ activation of AMP kinase in underlying vascular smooth muscle cells.[36] Others have used the same model to show that PVAT-derived leptin and angiopoietin-related protein 2 (Anptl2), both of which are upregulated with obesity or aging, contribute to excessive neointimal hyperplasia in response to vessel injury.[52,55] These studies have great clinical relevance for the study of diabetic and obese patients undergoing percutaneous coronary interventions.

Recently, Ohman et al[70] published a study in which they transplanted VAT to the common carotid artery of apolipoprotein E–deficient (Apoe$^{-/-}$) mice. This location is generally free of spontaneous atherosclerosis. Therefore, they hypothesized that transplantation of VAT to the carotid artery would incite atherosclerosis. They did indeed see a dramatic increase in complex atherosclerotic plaques in the underlying carotid artery. Before the development of atherosclerosis, they observed decreased vasodilator responses to acetylcholine in the transplanted arteries.[70] These effects were not observed with the transplantation of SAT and were associated with an increase in circulating MCP-1. Furthermore, they were abrogated in mice with whole body deficiency of P-selectin glycoprotein ligand-1 (Psgl-1) or with treatment with antibodies against Psgl-1.[70] It is still not understood whether Psgl-1 is acting on the intimal endothelium, or on endothelium within the adventitial vasa vasorum to initiate vascular disease. Limitations aside, these studies provide important proof of concept that PVAT can have both protective and pathological effects, and there is likely to be an increase in the use of these interesting experimental models.

Regarding the primary effect of PVAT on vascular disease, the most definitive study to date was recently published by Chang et al,[30] who describe a "PVAT-less" mouse. After generating a conditional knock-out of peroxisome proliferator-activated receptor-γ in vascular smooth muscle cells (SMPG-KO), the authors serendipitously found that these mice lacked PVAT. They went on to cross this mouse with Apoe$^{-/-}$ mice to pose the question: Is PVAT protective against the development of atherosclerosis? In thermo-neutral conditions, there was no difference in aortic atherosclerosis between wild-type and SMPG-KO/Apoe$^{-/-}$ mice.[30] However, the authors then exposed each strain of mice to the cold and noted a dramatic effect of cold conditions in limiting the extent of atherosclerosis in Apoe$^{-/-}$ mice. This effect was lost in the mice without PVAT (SMPG-KO/Apoe$^{-/-}$). Among the putative factors responsible for this effect, the authors showed that PVAT-derived prostacyclin (1) decreased with age and (2) decreased with high-fat diet and atherosclerosis and that (3) blockade of the prostacyclin receptor prevented

PVAT-derived inhibition of acetylcholine-induced vasoconstriction.[30] The authors concluded that PVAT-derived prostacyclin prevented acetylcholine-induced endothelial dysfunction, which is a precursor to atherosclerosis (Figure 2). The fact that the production of prostacylin was increased by active thermogenesis of PVAT suggests that there is an important role for BAT in the perivascular niche and supports the ongoing efforts to discover and promote such a depot in humans.

Summary of Basic Research

There is increasing evidence from studies in animals and humans that PVAT has beneficial effects on the vasculature under normal conditions and pathological effects under obese or diseased conditions (Figure 2). ADIPOQ is primary among the beneficial adipokines released from PVAT, signaling through smooth muscle AMP-regulated protein kinase to prevent proliferation and endothelial Akt to promote eNOS coupling and NOS generation. Beneficial paracine mediators also include lipid species such as palmitic acid methyl ester and prostacylin (Table 1). Obesity abrogates beneficial adipokine signaling, likely by stimulating inflammation of PVAT and increasing local cytokine production, thus inducing resistance to Akt and mTOR signaling. Resistance in these pathways results in eNOS uncoupling and increased local ROS production, smooth muscle cell proliferation, and increased smooth muscle cell tone by calcium-dependent mechanisms (Figure 2). This paracrine signaling may also function from the "inside out," as local ROS may generate ligands (4HNE) for peroxisome proliferator-activated receptor-γ in perivascular adipocytes, which signal the need for increased vasodilatory ADIPOQ production (Figure 2).[38] Direct manipulation of these pathways via pharmacological and nonpharmacological methods is likely to be a very effective means to combat CVD associated with obesity and will be an increasingly popular topic of research in the future.

Clinical Studies That Associate PVAT or EAT and CV Risk

Anatomy, Imaging, and Normal Values

There is confusion in the literature in regard to the nomenclature of cardiac fat depots and the methods section of imaging studies should be read carefully to understand what specific depot has been measured.[72] *Paracardial* fat is found on the external surface of the parietal pericardium and is also known as mediastinal or thoracic fat (Figure 1).[73] In contrast, *pericardial* adipose tissue (PAT) has been proposed to include the paracardial *and* epicardial fat together.[26] EAT lies beneath the visceral pericardium directly opposed to the surface of the

heart and encases the epicardial coronary arteries. EAT is the true visceral fat depot for the heart and shares the same developmental origin as mesenteric and omental fat, which are derived from the splanchnopleuric mesoderm.[74,75] Paracardial fat, however, is derived from the primitive thoracic mesenchyme, which also gives rise to the parietal pericardium.[74] In keeping with these different developmental origins, EAT is supplied by branches of the coronary arteries, whereas paracardial fat is supplied by the pericardiophrenic artery.[74]

There is growing interest in the imaging of EAT and PAT as a proxy measure of visceral adiposity. A second purpose of imaging EAT and PAT is to provide an incremental risk of incident CVD in addition to other risk factors. The repeated observation that EAT volumes correlate highly and directly with VAT volumes has strengthened interest in imaging for this purpose.[5,26,76–79] Furthermore, recent data suggest that there are individuals with normal VAT volume but increased PVAT volume; these patients may represent a unique subset of the "normal weight" obese.[80] Finally, and perhaps the most promising indication, involves imaging of EAT to follow treatment (eg, weight loss intervention studies).[81] Unfortunately, the vast majority of clinical studies are cross-sectional, and basic or translational studies are correlative, providing no information regarding causation. This is due primarily to 3 factors: mice do not have epicardial fat, depot-specific adipose tissue knockouts have only recently been developed, and normal human subjects are usually absent in molecular studies.[30,82] For purposes of CV risk stratification, measurement of EAT thickness using echocardiography has generally been the study of choice, due to its lesser cost, ease of use, and absence of radiation. CT has the advantage of simultaneous determination of coronary calcium, however, it is difficult to differentiate between epicardial and pericardial fat on CT.[83] MRI provides the most specific and precise measurements of epicardial fat volume. Unlike CT and MRI, there is some consensus regarding the method of measurement and normal values by 2-dimensional echocardiography. Epicardial fat thickness on the lateral wall of the right ventricle should be measured in the right parasternal long-axis view, perpendicular to the aortic annulus.[6] The EAT thickness extends from the outer wall of the right ventricle to the visceral layer of pericardium and is generally echo free. Mindful of the limitations of this measurement, a normal value is <7 mm.[6,84] Certainly, estimations of EAT volume by using MRI or CT will more accurately and precisely measure total fat mass, as will emerging 3-dimensional echocardiographic techniques. In addition to the quantity of adipose tissue, measurement of CT attenuation allows for the "quality" of fat to be imaged.[85] Lower CT attenuation (more negative Hounsfield units) is thought to represent increased lipid content and possibly greater metabolic risk. Recent data from the Framingham Heart Study showed that lower CT

attenuation is associated with an increased risk of insulin resistance and metabolic syndrome, after controlling for VAT volume.[85] In the following sections, we will review the evidence for imaging of EAT and PAT for the estimation of global CV risk and prognosis in CAD and atrial fibrillation (AF).

Global CV Risk and CAD

For the purposes of cardiometabolic risk, there is no question that EAT volume is highly and directly correlated with VAT[5,26,76–79] (Table 3). As a proxy measurement of VAT, which is not available without using CT or MRI, measurement of EAT thickness has inherent value over imprecise anthropometric estimations such as BMI or WC. However, the evidence to date does not suggest that increased EAT volume imparts additive risk when VAT mass is accounted for.

For example, in a cross-sectional CT study of 1155 Framingham Heart Study patients, PAT was highly correlated with VAT and components of the metabolic syndrome such as high triglyceride , low HDL cholesterol, and hypertension.[92] Yet, these correlations did not persist after adjustment for VAT, and VAT showed the strongest independent correlation.[92]

EAT thickness or PAT volume has subsequently been associated with multiple independent cardiac risk factors, such as fasting glucose, C-reactive protein, low HDL, carotid intima-media thickness, and others (Table 3).[76,86,92] However, when adjusted for VAT, many of these associations are diminished or absent. Perhaps the most definitive study to date was recent prospective study published by the Framingham Heart Study, in which 3000 patients free of CVD had PAT, thoracic aortic PVAT, and VAT measured at baseline and were followed for a median of 5 years to determine incident CV death, cancer, and all-cause mortality.[91] After multivariate adjustment, VAT, but not thoracic PVAT or PAT, was associated with incident CVD and cancer. There was no discriminatory power for all-cause mortality.[91]

Interestingly, a consistent finding in many of these studies is the association of coronary artery calcification with PAT volume, even after adjustment for VAT.[83,93] Therefore, even though many of the systemic determinants of CV risk associated with EAT are actually mediated by VAT, EAT and/or PAT may have local effects that promote vascular calcification or atherosclerosis.[83,93] One might speculate that alterations in PVAT surrounding the thoracic aorta influence the vascular stiffening or calcification that is associated with aging.

Cross-sectional studies have shown an association between prevalent CAD and PAT volume by CT and/or EAT thickness by using echocardiography[83,88,92] (Table 4). Fewer studies have correlated EAT with incident CAD. A recent study compared EAT volume in patients who developed incidental coronary calcium on a subsequent CT within 3 to 5 years.[90] EAT volume was compared at baseline and follow-up in cases and controls. There was no difference in the change in EAT volume indexed to body surface area between these 2 groups (4.9 ± 8.9 cm^3 versus 4.2 ± 8.0 cm^3, P=0.67) at follow-up.[90] The authors concluded that in low-risk patients (coronary calcium score of 0), EAT volume at baseline and increase over 3 to 5 years was not related to incident CAD.[90] The same group performed a second study in 375 intermediate-risk patients. Patients were divided into tertiles of coronary calcium progression between the performance of 2 CT scans 3 to 5 years apart, and low progressors were compared with high progressors.[98] Although there were no differences at baseline, at follow-up, high progressors had a greater volume of EAT than low progressors (102 ± 38 cm^3 versus 90 ± 35 cm^3, P=0.03).[98] In contrast to low-risk patients, EAT may influence the progression of CAD in intermediate-risk patients.[98] Finally, a recent case-control study reported that increased EAT volume was associated with greater major adverse cardiac events within 4 years.[87] After having a noncontrast CT scan, 2751 asymptomatic patients without known CAD were followed for 4 years. After adjustment for the Framingham Risk Score, coronary calcium score, and BMI, PAT volume was associated with an OR of 1.74 (95% CI 1.0 to 2.95 for each doubling of PAT) for major adverse cardiac events within 4 years.[87]

Atrial Fibrillation

Although less numerous, the evidence for a local effect of EAT and PAT in the pathogenesis of AF is more compelling (Table 5). It is well known that obesity is a risk factor for new-onset AF.[103] Considering the increasing incidence of obesity and the aging of the population, prevalent cases of AF are expected to exceed 10 million persons in the United States by 2050.[104] Recent data from the Framingham Heart Study have shown that PAT volume, but not intrathoracic or VAT, is associated with prevalent AF.[101] In age- and sex-adjusted models, per 1-SD increase in PAT volume, there was a 30% increased risk of AF (OR 1.30, 95% 1.0 to 1.6, P<0.02). This association was not observed for VAT or thoracic fat volume. Furthermore, it remained equally significant in multivariable models, which included measures of visceral adiposity such as BMI.[101] This is in contrast to many of the prior studies of CV risk in which the observed associations with PAT volume are negated when the systemic effects of visceral adiposity are accounted for. The authors concluded that PAT likely exerts a local effect on the atria, by secreting cytokines/adipokines that affect atrial mechanical or electrical remodeling; this possibility is supported by the results of translational studies.[50,101]

Table 3. Studies Examining the Relationship Between EAT and/or PAT and Cardiovascular Risk Factors

Authors	Fat Depot	Imaging Modality	Clinical Variables	Measure of Association	Notes
Iacobellis et al[78]	EAT	Echo	WC VAT volume	r=0.845, P<0.01 r=0.840, P<0.01	72 patients with a BMI ranging from 22 to 47 kg/m².
Wheeler et al[26]	PAT	CT	VAT volume	r=0.81, P<0.0001	80 subjects chosen at random from a family study of sibling pairs with type 2 diabetes mellitus.
Iacobellis et al[86]	EAT	Echo	VAT volume IMT	r=0.85, P<0.001 r=0.78, P<0.001	60 HIV+ patients with HAART-associated metabolic syndrome. IMT was greater in patients with metabolic syndrome, than those without.
Iacobellis et al[77]	EAT	Echo	VAT volume Serum AST Serum ALT Serum adiponectin	r=0.83, P<0.01 r=0.56, P<0.01 r=0.58, P<0.01 r=−0.45, P<0.01	57 HIV+ patients with HAART-associated metabolic syndrome. EAT thickness was associated with visceral fat volume by MRI and serum markers of hepatic steatosis (AST, ALT).
Wang et al[79]	EAT (left AV groove)	CT	Resistin hsCRP	r=0.16, P<0.05 r=0.16, P<0.05	148 consecutive patients undergoing MDCT. Researchers measured thickness of EAT in different areas. EAT thickness in the left AV groove was the only measurement associated with all 3 components of the metabolic syndrome.
Cheng et al[87]	PAT	CT	MACE	OR 1.7 (95% CI 1.0 to 2.9) per doubling of PAT volume	2751 asymptomatic patients without CAD who had MDCT and were followed for major adverse cardiac events for 4 years. Multivariate analysis was adjusted for BMI, CCS, and Framingham scores.
Dey et al[88]	PAT	CT	VAT area BMI	r=0.79, P<0.0001 r=0.49, P<0.0001	201 patients who had CT scans to measure CCS. PAT volume was also associated with coronary calcium (OR 3.1, P=0.04).
Tamarappo et al[89]	PAT	CT SPECT	Ischemia	OR 2.9 (95% CI 1.5 to 5.5), P<0.001	1777 consecutive patients without previously known CAD who had CT performed within 6 months of SPECT. Multivariable analysis was adjusted for BMI, CCS, and traditional risk factors but not VAT.
Otaki et al[90]	EAT	CT	Incident CAD	ND	1248 low-risk patients with CCS of 0 who developed coronary calcium, and 106 controls who did not. There was no difference in the indexed EAT volume in those with and without incident coronary calcium.
Britton et al[91]	VAT PAT Aortic PVAT	CT	Incident CVD Cancer All-cause mortality	HR 1.44 (95% CI 1.08 to 1.97), P=0.01 HR 1.42 (95% CI 1.12 to 1.84), P=0.005	Prospective study that measured fat depot in 3000 patients without CVD at baseline; median follow-up of 5 years. VAT, but not PAT or PVAT from the thoracic aorta, was associated with an incidence CVD and cancer. None of the fat depots were associated with all-cause mortality.

EAT indicates epicardial adipose tissue; PAT, pericardial adipose tissue; Echo, echocardiography; WC, waist circumference; VAT, visceral adipose tissue; BMI, body mass index; CT, computed tomography; HIV, human immunodeficiency virus; IMT, intima-media thickness; HAART, highly active anti retroviral therapy; ALT, alanine aminotransferase; AST, aspartate aminotransferase; MRI, magnetic resonance imaging; AV, atrioventricular; hsCRP, high-sensitivity C-reactive protein; MDCT, multidetector computed tomography; MACE, major adverse cardiac events; SPECT, single-photon emission computed tomography; CAD, coronary artery disease; CCS, coronary calcium score; HR, hazard ratio; ND, no difference; PVAT, perivascular adipose tissue.

Table 4. Studies That Examine the Relationship Between Coronary Atherosclerosis and EAT or PAT

Authors	Fat Depot	Imaging Modality	Clinical Variables	Measure of Association	Notes
Ding et al[94]	PAT	CT	CAC (+/−)	OR 1.92 (95% CI 1.2 to 2.9), $P<0.002$	162 patients from the Multi-Ethnic Study of Atherosclerosis. Per 1-SD increment in PAT volume, there was a 92% greater risk of the presence of CAC. Model was adjusted for height but not VAT.
Jeong et al[95]	EAT	Echo	Age CRP BMI WC	$r=0.33$, $P<0.0001$ $r=0.18$, $P=0.009$ $r=0.14$, $P=0.042$ $r=0.22$, $P=0.001$	203 consecutive patients who had both echocardiography and diagnostic coronary angiography. Per 1-SD increase in EAT thickness, there was an OR of 10.53 for significant coronary stenosis. Multivariate analysis was not adjusted.
Mahabadi et al[96]	PAT	CT	Prevalent CVD Prevalent CHD Prevalent MI	OR 1.3 (95% CI 1.0 to 1.5), $P<0.006$ OR 1.9 (95% CI 1.2 to 3.0), $P<0.004$ OR 1.3 (95% CI 1.0 to 1.8), $P<0.03$	1267 participants in the Framingham Offspring Cohort (9.7% prevalent CVD). PAT and VAT volume were associated with prevalent CVD. However, PAT, but not VAT, was also associated with prevalent CHD or MI.
Grief et al[92]	PAT	CT	Diseased segments Serum adiponectin Serum HDL Serum hsCRP Serum TNFα	$r=0.44$, $P<0.0001$ $r=-0.23$, $P<0.0001$ $r=-0.25$, $P<0.0001$ $r=0.12$, $P<0.04$ $r=0.18$, $P<0.002$	286 consecutive patients with intermediate risk of CAD. PAT volume was significantly associated with BMI and the number of diseased segments, independent of BMI. VAT was not measured.
Saam et al[97]	PAT	FDG PET CT	Target-to-background ratio in LAD	$r=0.20$, $P<0.05$	292 cancer patients who had FDG PET and CT scans. Inflammation in the LAD, as measured by FDG uptake, correlated with HTN, BMI, CAD, and PAT volume.
Liu et al[83]	PAT	CT	HTN MS CAC	OR 1.3 (95% CI 1.0 to 1.9), $P<0.03$ OR 1.3 (95% CI 1.0 to 1.6), $P<0.006$ OR 1.3 (95% CI 1.1 to 1.6), $P<0.004$	1414 patients enrolled in the Jackson Heart Study. Correlations of PAT volume with cardiac risk factors were diminished after adjustment for VAT volume. However, associations with HTN, MS, and CAC remained significant.
Cheng et al[87]	PAT	CT	MACE	OR 1.7 (95% CI 1.0 to 2.9) per doubling of PAT volume	2751 asymptomatic patients without CAD who had MDCT and were followed for MACE for 4 years. Multivariate analysis was adjusted for BMI, CCS, and Framingham scores.
Dey et al[88]	PAT	CT	VAT area BMI	$r=0.79$, $P<0.0001$ $r=0.49$, $P<0.0001$	201 patients who had CT scans to measure CCS. PAT volume was also associated with coronary calcium (OR 3.1, $P=0.04$).
Tamarappo et al[89]	PAT	CT SPECT	Ischemia	OR 2.9 (95% CI 1.5 to 5.5), $P<0.001$	1777 consecutive patients without previously known CAD who had CT performed within 6 months of SPECT. Multivariable analysis was adjusted for BMI, CCS, and traditional risk factors but not VAT.
Otaki et al[90]	EAT	CT	Incident CAD	ND	1248 low-risk patients with CCS of 0 who developed coronary calcium, and 106 controls who did not. There was no difference in the indexed EAT volume in those with and without incident coronary calcium.

EAT indicates epicardial adipose tissue; PAT, pericardial adipose tissue; CT, computed tomography; CAC, coronary artery calcium; Echo, echocardiography; VAT, visceral adipose tissue; CRP, C-reactive protein; BMI, body mass index; WC, waist circumference; CVD, cardiovascular disease; CHD, coronary heart disease; MI, myocardial infarction; HDL, high-density lipoprotein; hsCRP, high-sensitivity C-reactive protein; TNFα, tumor necrosis factor α; FDG, fluorodeoxyglucose; PET, positron emission tomography; LAD, left anterior descending coronary artery; HTN, hypertension; CAD, coronary artery disease; ND, no difference; MS, metabolic syndrome; MACE, major adverse cardiac events; CCS, coronary calcium score; SPECT, single-photon emission computed tomography; MDCT, multidetector computed tomography.

Table 5. Studies That Report an Association Between EAT and/or PAT and AF

Authors	Fat Depot	Imaging Modality	Clinical variables	Measure of Association	Notes
Shin et al[99]	EAT	CT	LAV Total EAT Periatrial EAT	NA NA NA	40 patients with PAF, 40 with PeAF, and 80 control patients without AF. PAF and PeAF patients had larger LAV, total EAT, and periatrial EAT than controls. PeAF patients had greater LAV, EAT total, and periatrial EAT and lower coronary sinus adiponectin than PAF patients.
Batal et al[100]	EAT	CT	AF burden	OR 5.30 (95% CI 1.3 to 20.2)	169 patients who had CT scans for AF or CAD. EAT thickness directly posterior to the LA was greater in those with PeAF than in those with PAF or without AF. Multivariate analysis controlled for age, BMI, and LA size.
Thanassoulis et al[101]	PAT	CT	Prevalent AF	OR 1.28 (95% CI 1.03 to 1.58)	Pericardial fat was associated with AF after adjustment for risk factors, including BMI
Wong et al[102]	PAT	MRI	Prevalent AF AF symptom burden AF chronicity AF recurrence	P<0.05 for all end points	PAT volumes were significantly associated with all 4 end points, even after adjustment for BMI and BSA. Total pericardial fat volume showed a modest, linear association with LA volume (r=0.46, P<0.001).

EAT indicates epicardial adipose tissue; PAT, pericardial adipose tissue; AF, atrial fibrillation; CT, computed tomography; LAV, left atrial volume; NA, not available; PAF, paroxysmal atrial fibrillation; PeAF, permanent atrial fibrillation; BMI, body mass index; LA, left atrium; MRI, magnetic resonance imaging; BSA, body surface area; CAD, coronary artery disease.

A second study, in which 169 patients who underwent CT scans for AF or CAD were examined, strengthened and refined this conclusion.[100] Thickness of epicardial fat pads around the mid-left atrium (LA) was measured in relation to 3 anatomical landmarks: the esophagus, pulmonary artery, and thoracic aorta. Of these 3 fat pads, mid-LA–esophagus is the most posterior to the LA and directly adjacent to the pulmonary vein ostia. Interestingly, in patients with persistent AF, thickness of the mid-LA–esophagus fat pad was almost twice that of those with paroxysmal or no AF (0.56 cm versus 0.39 cm, P=0.011, and 0.56 cm versus 0.34 cm, P<0.015).[100] In contrast, there was no difference in the thickness of the anterior epicardial fat pads (mid-LA–thoracic aorta, mid-LA–pulmonary artery) between groups. In multivariate analysis, adjusted for age, BMI, and mid-LA area, thickness of the mid-LA–esophagus epicardial fat was a significant predictor of AF burden (OR 5.30, 95% CI 1.39 to 20.24, P=0.015).[100]

A recent MRI study confirmed these results by showing that PAT volume is associated not only with prevalent AF and AF burden but also LA remodeling and poorer outcomes after radiofrequency ablation.[102] A total of 110 patients undergoing RF ablation for AF and 20 normal controls underwent MRI to quantify PAT volumes. There was a dose-response of PAT volume for both the presence and the chronicity of AF; those with persistent AF had the highest mean PAT volume and normal controls had the lowest. After adjustment for body weight, total PAT volume was predictive of the presence of AF

(OR 13.28, 95% CI 2.2 to 79, P=0.005) and the presence of nonparoxysmal AF (OR 3.28, 95% CI 1.2 to 8.5, P=0.015), whereas BMI was not.[102] Importantly, PAT volume, but not BMI, was also associated with greater LA volume and predicted of AF recurrence.

Although these studies still demonstrate association and not causation, they do provide compelling evidence that epicardial fat depots may have an adverse effect on the adjacent atrial or pulmonary vein tissue. Furthermore, because many of these studies control for measures of visceral adiposity, they suggest that these effects are specific to EAT/PAT and not systemic inflammation. This is may be analogous to the independent association of EAT/PAT with coronary calcification.[83,93]

Ventricular Remodeling and Heart Failure

In patients without CVD, EAT thickness measured by using echocardiography has been found to directly correlate with indexed left ventricular (LV) mass (r=0.75, P=0.01).[105] When classified by waist circumference, men and women with abdominal obesity had greater LV mass and EAT thickness than those with truncal obesity. In multivariate analysis, EAT thickness was the strongest determinant of indexed LV mass.[105] In contrast, 2 recent studies have demonstrated that patients with systolic heart failure (HF) have proportional reductions in EAT volume compared with normal controls.[106,107] In the first study, 381 patients referred for

myocardial perfusion imaging had CT performed. Patients were divided into those with or without a history of LV dysfunction (ejection fraction <55%) on echocardiography. Patients with reduced ejection fraction had lower EAT volumes than control patients (114.5 ± 98.5 cm^3 versus 83.5 ± 98.5 cm^3, $P<0.05$). In subgroup analysis, patients with a severely reduced ejection fraction (<35%) had EAT volumes that were lower than those with moderate LV dysfunction.[106] These differences in EAT volume persisted when adjusted for BMI. Correlations with LV mass indices were not provided. A second study used MRI to measure EAT volume in 66 patients with cardiomyopathy and 32 healthy controls.[107] Indexed EAT volume showed a direct correlation with indexed LV end-diastolic mass in both normal controls and HF patients. However, on average, HF patients had less indexed EAT mass than normal controls (22 ± 5 g/m^2 versus 34 ± 4 g/m^2, $P<0.001$).[107] The ratio of EAT mass to LV mass was also significantly reduced in HF patients compared with controls. Post-mortem studies have also shown a significant reduction in EAT in patients with evidence of HF.[108] As the ratio of EAT to myocardium generally remains constant in normal individuals, the authors suggested that there is a "deficit" of epicardial fat in HF patients.[107] As has been shown in obesity or CAD, this may be associated with reductions in local or serum ADIPOQ concentrations, a cardioprotective adipokine that has anti-inflammatory and vasodilatory effects.[107]

Summary

Increased EAT thickness measured by using echocardiography or EAT/PAT volume by using CT/MRI correlates well with visceral adiposity and hence is associated with multiple components of the metabolic syndrome. Although increased EAT volume is associated with prevalent CAD, this association is most likely due to the systemic inflammation caused by hypertrophied visceral fat depots. There is no strong evidence to date that EAT or PVAT in humans is independently associated with incident CVD. However, EAT may have local paracrine effects on the heart and circulation, as shown by the independent association of EAT volume with coronary calcification, LA volume, AF presence, and burden. This possibility seems increasingly likely in light of evidence that EAT from patients with CAD has increased inflammatory cytokine expression at the tissue level, without evidence of increased proinflammatory cytokines in serum.[49] The observation that patients with systolic HF have reduced EAT volume suggests that there may be a beneficial effect of EAT that is lost in systolic dysfunction. Whether this correlates with reduced tissue or plasma levels of cardioprotective adipokines such as ADIPOQ has yet to be demonstrated, and it may also be a manifestation of cardiac cachexia. Certainly, there is ample evidence to suggest that EAT and PAT are potential therapeutic targets that could be modified to affect health or disease. For example, diet, exercise, and gastric bypass have all been shown to reduce visceral and epicardial fat mass and lower cardiometabolic risk.[81,109,110] Additional experimental therapeutic strategies may include drugs that inhibit EAT/PAT inflammation, epicardial/pericardial fat removal or transplantation, and stem cell–based protocols in chronic systolic HF.

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