ARTICLE

Role of Perivascular Adipose Tissue and Exercise on Arterial Function with Obesity

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[1]Biological Sciences, School of Biological Sciences, University of Reading, Reading, UK; [2]Department of Human Performance, Division of Exercise Physiology, School of Medicine, West Virginia University; and [3]West Virginia Clinical and Translational Science Institute (WVCTSI), Morgantown, WV

BOATENG, S.Y., I.M. OLFERT, and P.D. CHANTLER. Role of perivascular adipose tissue and exercise on arterial function with obesity. *Exerc. Sport Sci. Rev.*, Vol. 49, No. 3, pp. 188–196, 2021. *Adipose tissue and arterial dysfunction are common in the obese state. Perivascular adipose tissue (PVAT) plays an important role in mediating arterial health, and with obesity, the PVAT dysfunction negatively affects arterial health. Exercise training exerts direct and beneficial effects on PVAT, providing an additional and novel pathway by which exercise can improve arterial health in diseased populations.* **Key Words:** obesity, exercise, arterial function, perivascular adipose tissue, exercise training

Key Points

- Obesity leads to a toxic perivascular adipose tissue (PVAT).
- PVAT mediates aortic function via paracrine and autocrine pathways.
- Exercise training improves PVAT phenotype and directly improves arterial function and structure with obesity.

INTRODUCTION

Overweight and obesity affect 42.4% of the U.S. population (1), which has significant cardiovascular (CV) consequences resulting in a reduced quality of life and increased mortality rate (2). Arterial disease is an important clinical pathological consequence of obesity with significant macro- (aorta, femoral, etc.) and microvasculature (arterioles) changes that negatively affect the function of multiple organs. Obesity also results in an excessive accumulation of adipose tissue surrounding most of the arterial network. This perivascular adipose tissue (PVAT) was initially thought to provide structural support; however, in 2002, Lohn *et al.* (3) demonstrated that PVAT from healthy subjects contains perivascular relaxing factors (PVRFs) that directly relaxed contracted arteries. Since then, various laboratories, including our own, have shown a direct effect of PVAT on arterial health and that with obesity, there is an excessive accumulation and a phenotypic change in PVAT (4,5).

It is well known that regular exercise exerts beneficial physiological changes to the arterial system and adipose tissue morphology. However, recently, my laboratory, and others, has suggested that exercise training exerts beneficial effects on PVAT with subsequent improved actions on arterial function/structure (6). As such, we hypothesized (Fig. 1) that obesity negatively alters PVAT phenotype, which directly induces arterial dysfunction, and that exercise training can limit the obesity-PVAT arterial dysfunction. This review will summarize the effects of obesity on adipose tissue depots, arterial health, and their interaction, and how regular exercise improves arterial health with obesity.

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ADIPOSE TISSUE MORPHOLOGY AND PATHOLOGY

In mammals, there are white (WAT), brown (BAT), and beige adipose tissue, which have distinct functions and different morphologies, protein expression patterns, and developmental origins. Adipose tissue is composed of adipocytes and a stromal vascular fraction consisting of pericytes, endothelial cells, monocytes, macrophages, and stem cells. Adipose tissue has an endocrine role, secreting adipokines such as leptin, angiotensin, adiponectin, tumor necrosis factor alpha (TNF-α), interleukin-6 (IL-6), etc. The function of WAT, which represents 10%–30% of body weight, is to store energy in the form of lipids, and they have few mitochondria but have large single lipid droplets of triacylglycerol. There are two main depots of WAT, the subcutaneous (SAT) depot (adipose tissue located under the skin) and the visceral (VAT) depot. SAT, which makes up a majority of the total fat mass, usually consists of smaller adipocytes that produce low levels of proinflammatory adipokines (7) and high anti-inflammatory adipokines (8).

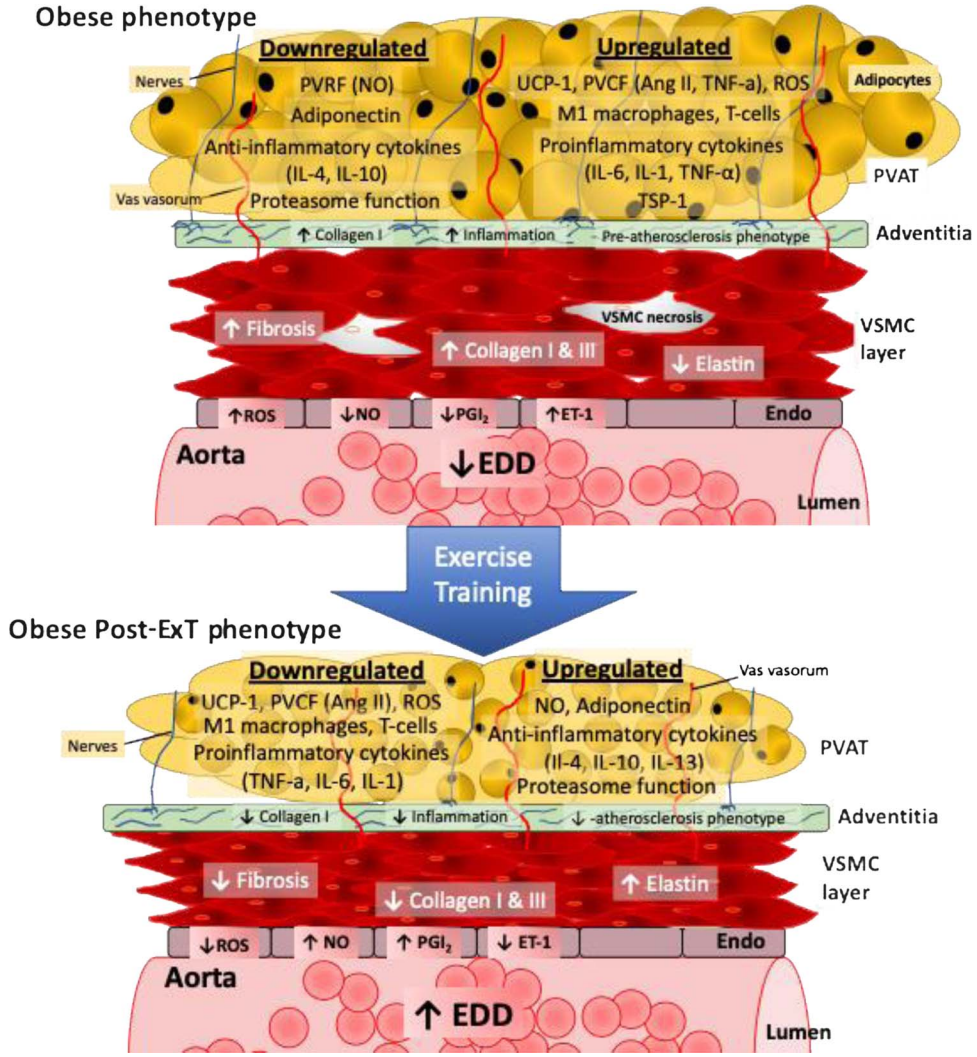

Figure 1. The role of obesity and exercise on PVAT-induced aortic (dys)function. With obesity, the PVAT becomes more white (decreased UCP-1) and dysfunctional, reflected by a greater infiltration of M1 macrophages and T cells with a corresponding increase in proinflammatory cytokines and ROS coupled with a downregulation in proteasome function and anti-inflammatory cytokines. This dysfunctional PVAT phenotype results in a decrease in PVRF (NO and adiponectin) and an increase in PVCF (ET-1 and Ang II). As PVAT is closely positioned to the vascular adventitia without an anatomic barrier, it can directly communicate with vascular cells by transferring cytokines. Furthermore, cytokines can be transferred through the vasa vasorum to VSMCs. As such, obesity increases collagen 1 content and inflammation to promote a preatherosclerotic phenotype in the adventitia. Significant changes also occur to the VSMC, reflected by an increase in fibrosis and collagen content, with a reduction in elastin content with more necrotic cells. In the endothelium, there is an impaired release of NO and PGI_2 with an increase in ROS and ET-1, which leads to reduced aortic EDD and increased stiffness. However, when obese animals are under exercise training (blue arrow), the dysfunctional PVAT is partly reversed. That is, obese ExT PVAT reflects a more brown-like phenotype, with reduced proinflammatory cytokines, ROS, and increased anti-inflammatory cytokines and proteasome function. Ultimately, exercise training improves PVRF and reduces PVCF so that aortic EDD and stiffness are improved. Ang II, angiotensin II; Endo, endothelium; EDD, endothelial dependent dilation; ET-1, endothelial-1; ExT, NO, nitric oxide; PGI2, prostacyclin; PVAT, perivascular adipose tissue; PVCF, perivascular-derived contraction factors; PVRF, perivascular relaxing factors;ROS, reactive oxygen species; UCP-1, uncoupling protein 1; VSCMs, vascular smooth muscle cells.

SAT acts as an energy store, a thermal insulator, a cushion against mechanical stress, and a physical barrier to infection (9). VAT is composed of unilocular adipocytes tightly packed together and supported by loose connective tissue with a dense network of capillaries. In contrast, BAT has unique thermogenic properties and is a vital organ for maintaining body temperature in smaller mammals and human infants. BAT has a polygonal shape and contains multiple smaller lipid droplets, expressing uncoupling protein 1 (UCP-1), Cidea, and peroxisome proliferator-activated receptor-γ coactivator. The degree of thermogenesis in BAT can be influenced by a cold environment, and BAT is highly vascularized and innervated. BAT was thought to only exist in children; however, BAT has been identified in adults (10). BAT has been found interspersed in WAT; however, they are not derived from the myf5 lineage (classical BAT) and thus are known as beige or brite cells. These cells have high UCP-1 expression; thus, beige fat can acquire a brown-like phenotype upon cold exposure or pharmacological stimulation. Both beige and brown adipocytes are important in regulating energy expenditure by reducing fat accumulation and improving metabolic health (11).

PVAT surrounds the adventitia of most arteries and represents around 3% of the total body adipose tissue mass. In addition to storing triglycerides, PVAT secretes a wide range of adipokines that have a direct impact on arterial health. It is suggested that PVAT release factors that reach the medial and

endothelial layers via direct diffusion through the vasa vasorum (12) or via a dense reticular network of collagenous conduits connecting the medial layer with the underlying adventitia (13). In lean rodents, the mesenteric, carotid, and femoral arteries are surrounded by white PVAT, whereas the thoracic aorta is surrounded by brown PVAT and the abdominal aorta by beige PVAT (14). Epicardial adipose tissue (EAT) is located between the visceral pericardium and makes direct contact with the coronary vasculature; thus, the EAT adipokines directly affect coronary function. Pericardial adipose tissue (PAT) on the other hand is located in and around the pericardial sac that surrounds the heart and should be considered an atypical PVAT depot. That is, although it does not make direct contact with the coronary vasculature, secreted adipokines reach the coronaries via the pericardial fluid (15). Figure 2 shows a simplified schematic of the different adipose tissue depots.

With obesity, the mature adipocytes undergo hyperplasia and hypertrophy. Hyperplasia of adipocytes is determined by the recruitment of preadipocytes within the tissue stroma, but the numbers of these are limited, suggesting that there is a limit to the degree to which adipocytes can expand by this means (37). In addition, adipocyte hypertrophy also is limited by their capacity to store triglycerides and, as such, results in excess triglycerides being stored in and around other tissues, including around the vasculature (16). Furthermore, reaching this threshold of hyperplasia and hypertrophy causes stress in adipocytes and the activation of Jun N-terminal kinase and nuclear factor-Kß (Nf-Kß) signaling pathways, which initiates an inflammatory response leading to local and systemic inflammation and impaired adipogenesis of precursor cells (24). In addition, there is a recruitment of monocytes to the adipose tissue, which differentiate to macrophages and amplify the inflammatory response (24). WAT is considered the most common fat depot responsible for the expansion of the adipose tissue; however, obesity also leads to maladaptive responses to BAT and PVAT. With obesity, there is an expansion of BAT through hyperplasia; however, this may be associated with a loss of its protective role due to reduced glucose uptake and thermogenesis (38). Indeed, BAT seems to adopt a white-like phenotype, with increased lipid accumulation (39).

The actions of obesity on PVAT are multifactorial, resulting in significant changes to its morphology, biochemistry, and physiology (40). With obesity, there is an increased release of adipokines (resistin, leptin, and visfatin), proinflammatory cytokines (IL-6, IL-1, TNF-α, etc.), and chemokines (RANTES, CCL5, MCP-1, and CCL2), with reduced anti-inflammatory cytokines (IL-10, IL-13, IL-4, etc.) from the PVAT (4). With obesity, the adipose tissue inflammation is accompanied by increased infiltration (41) and phenotypic switching of macrophages to a proinflammatory activation profile (42). Furthermore, $CD8^+$ T cells produce monocyte chemoattractant proteins (MCPs), which modulate the infiltration of macrophages in PVAT (43). Furthermore, cytotoxic $CD8^+$ T cells secrete TNF-α, IL-2, interferon-γ, whereas treatment of obese mice with CD8-specific antibodies was shown to attenuate M1 macrophage infiltration and adipose tissue inflammation (44). In this regard, inflammatory cells in PVAT are implicated in the recruitment and proliferation of adventitial myofibroblasts. Similarly, the EAT changes with obesity are characterized by hypertrophy, failure to store triglycerides, increased lipolysis, and inflammation (45). As EAT expands, it becomes hypoxic and dysfunctional and is invaded by increased numbers of macrophages and T lymphocytes, resulting in a shift in its metabolic profile (46). The result is increased secretion of proinflammatory cytokines that contribute to the inflammatory environment characteristic of atherogenesis (29), as well as reduced secretion of antiatherosclerotic adipokines such as adiponectin (25). In this setting, the

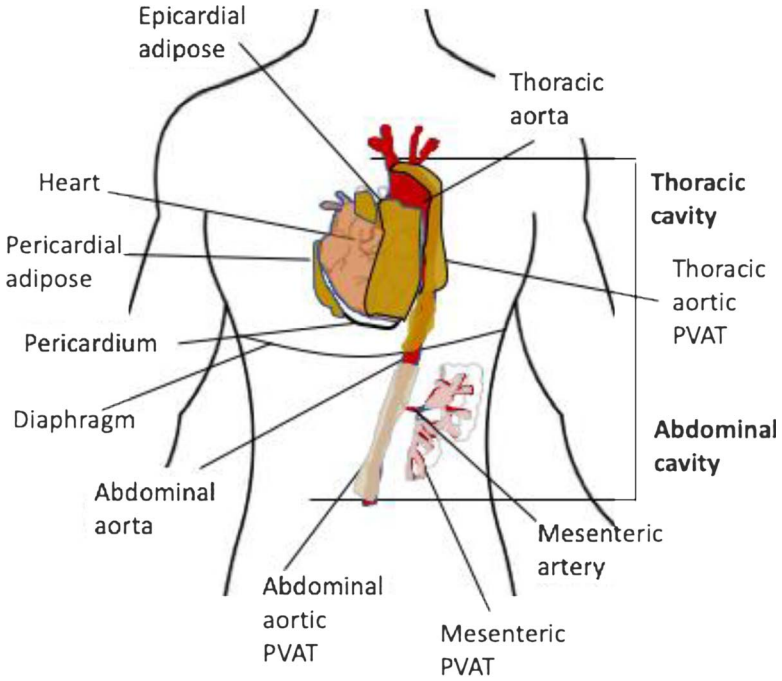

Figure 2. Typical and atypical perivascular adipose tissue (PVAT) distribution in humans. Diagram shows the location of typical and atypical PVAT depots in humans. The color differences reflect the different degrees of brown adipocytes in the adipose tissue. Further changes associated with obesity and exercise are described in the Table.

TABLE. Typical and atypical PVAT phenotype in lean, obesity, and after exercise

Adipose Tissue Type	Normal/Lean	Obese	Exercise	References
Mesenteric PVAT	Low UCP-1/thermogenesis	Thermogenesis ↓ Leptin ↑ Adipocyte hypertrophy	Tissue volume ↓ Thermogenesis ↑	(14,16–20)
Abdominal PVAT	Medium UCP-1 thermogenesis	Thermogenesis ↓ Leptin ↑ Adipocyte hypertrophy	Tissue volume ↓ Thermogenesis ↑	(14,21–23)
Thoracic PVAT	High UCP-1/thermogenesis Protective	Thermogenesis ↓ Leptin ↑ Adipocyte hypertrophy	Tissue volume ↓ Thermogenesis ↑ Inflammation ↓	(4,6,14,21,23,24)
PAT	High UCP-1/thermogenesis Protective low inflammation	Thermogenesis High inflammation Leptin ↑ Adipocyte hypertrophy/hyperplasia?	Tissue volume ↓ Thermogenesis? Inflammation?	(25–28)
EAT	UCP-1 expression High thermogenesis Protective low inflammation	Thermogenesis ↓ Function: lipid uptake/ less protective Leptin ↑ Adipose hyperplasia	Tissue volume ↓ Thermogenesis ↑ Inflammation ↓	(29–36)

EAT, epicardial adipose tissue; PAT, pericardial adipose tissue; PVAT, perivascular adipose tissue; UCP-1, uncoupling protein 1.

beneficial paracrine effects of EAT are lost, and such dysfunctional changes may play a causative role in local inflammation, with the potential to influence the development and progression of coronary artery plaque (30).

Unlike PVAT, our understanding as to how obesity impacts PAT phenotype is limited. Excessive adipose tissue around the heart is associated with obesity (31), leading to atrial fibrillation and calcification of the coronary vessels (26). Our most recent work in mice suggests that PAT has characteristics more similar to beige and BAT rather than WAT. Fatty acid binding protein 4, leptin, and adiponectin mRNA levels were all significantly lower in PAT than in visceral WAT, whereas UCP-1, iodothyronine deiodinase 2 (DIO2), and cytochrome c oxidase subunit 8B were higher (27). This may suggest that PAT has increased flux through oxidative phosphorylation and the electron transport chain, although UCP-1 and DIO2 are more associated with increased thermogenesis (47). These data suggest that PAT has a beige or BAT phenotype, which would usually be considered protective. However, despite PAT having more of a BAT gene signature, we also found some significant differences between the two depots, particularly with TNF-α, which was higher in PAT. High-fat feeding also increased IL-6 only in PAT compared with VAT. These data suggest that PAT may be more prone to metabolic dysfunction as a result of proinflammatory macrophage infiltration after high-fat feeding and obesity. Following obesity, PAT also showed the largest increase in cellularity, suggesting that this depot expands to a large degree through adipocyte hypertrophy (27). These data all indicate that many types of adipose depots at different locations (PAT, EAT, PVAT, etc.) can be negatively influenced by obesity with potentially severe implications on arterial health.

OBESITY AND ARTERIAL HEALTH

Arterial Function

One of the earliest manifestations of arterial disease with obesity is endothelial dysfunction. Indeed, an increase in body mass index (BMI) was an independent negative predictor of brachial endothelial dependent dilation (EDD; flow-mediated dilation) (48). Even the resistance vessels isolated from a biopsy of abdominal SAT of patients with severe obesity showed a dramatic reduction in EDD compared with lean controls (49).

We have used the obese Zucker rat (OZR) model to show that aortic EDD to methacholine is significantly impaired (between 15% and 20%) in male and female OZRs versus lean controls (4,50). However, endothelial independent dilation to sodium nitroprusside, which results in the direct stimulation of the vascular smooth muscle cells (VSMCs) is not affected by obesity (4,50). Similar findings have been noted in mouse models of obesity (high-fat diet) with regard to EDD and EID (51). Furthermore, we and others have consistently identified that the EDD of the muscular resistance arterioles is significantly impaired in obese versus lean rats (52,53). Similarly, the EDD of the middle cerebral artery (MCA) is decreased (−8% to −20%) in obese male and female rats/mice and that the degree of impairment accompanied the severity of obesity (50,54). The dysfunctional resistance arterioles with obesity result in perfusion limitations (53) and greater injury from ischemic strokes (55).

What is inducing this obese arterial phenotype? Under normal physiological conditions, the secretion and release of endothelial-derived vasoactive factors are maintained and balanced. However, with obesity, there is a reduction in arterial nitric oxide (NO) and prostacyclin and an increase in endothelial-1 (ET-1) and thromboxane release (56). Inflammation and oxidative stress are proposed as the underlying factors that are inducing this imbalance. We have shown that circulating and tissue (aorta and MCA) levels of nitrotyrosine and TNF-α are elevated one- to threefold in obese rats (4,6,50,54). As such, the obesity-related decline in endothelial function is linked to the excessive oxidative stress (superoxide anion, hydroxyl racial, lipid radicals, etc.); however, the antioxidant defense pathway also is reduced with obesity (57). As such, the excessive production of superoxides leads to rapid reaction with NO to form peroxynitrite and thus reduces NO bioavailability and causes nitrosylation of proteins. Importantly, endothelial dysfunction in the aorta or resistance vessel returns to near normal healthy levels with the acute incubation of the vessels (*ex vivo*) with the antioxidant Tempol (6,58). Furthermore, the daily delivery of Tempol in the drinking water of obese rats significantly lowered circulating nitrotyrosine and TNF-α, improved aortic NO bioavailability, and mostly restored EDD

of the MCA in obese rats (58). Obesity also is associated with increased activation of the renin-angiotensin system and increased concentrations of angiotensin II that can further promote oxidative stress in vessels and impair arterial function (59). Other factors influencing NO bioavailability, such as diminished sensitivity of endothelium to insulin (60), or obesity-mediated alterations in matricellular proteins (such as thrombospondin-1 (TSP-1)) (61) that can directly impair the NO synthesis pathway (62), also are likely to work in concert and further contribute to arterial dysfunction.

Arterial Remodeling

The transition from being healthy to having obesity/metabolic diseases coincides with an increase in carotid intima medial thickness (0.011 vs 0.005 $mm \cdot yr^{-1}$) and lumen diameter (0.055 vs 0.023 $mm \cdot yr^{-1}$) (63). The remodeling of the large arteries in response to obesity is largely due to an increase in circumferential wall stress and flow-mediated shear stress (64). Thus, the arteries undergo changes in either lumen size or arterial wall thickness to maintain tensile wall stress within ideal limits. Animal models also demonstrate that the conduit vessels undergo remodeling similar to that noted in obese humans (65). Clinical data also suggest that the aorta undergoes some form of remodeling with obesity. A large population of subjects, free from CV risk factors, showed that increasing BMI was associated with increasing aortic size (66). In addition to large artery remodeling, small resistance arteries dissected from the abdominal SAT of obese individuals had increased wall thickness and media-to-lumen ratio compared with healthy controls, indicating hypertrophic remodeling (67). Studies in the OZR showed atrophic remodeling (reduced lumen size and thinner vascular walls) of the microvasculature (68). There also is a profound reduction in microvessel density, which negatively impacts mass transport and exchange with the surrounding parenchymal tissues within skeletal muscle (69). Furthermore, conduit and resistance vessels become stiffer with obesity. Results from a prospective cohort study showed that central obesity predicted the development of arterial stiffness over a period of 16 yr (70).

Structural changes to the extracellular matrix directly impacts arterial stiffening. Mouse models of obesity are known to induce arterial stiffness (71). An accumulation of arterial collagen content (which are 100–1000 times stiffer than elastin) is noted with obesity, which is linked to increased transforming growth factor-ß (TGF-ß) signaling and mineralocorticoid receptor activation (72), and that mineralocorticoid receptor blockade can prevent the diet-induced arterial stiffness (72). In addition to the collagen accumulation, a high-fat, high-refined carbohydrate Western diet resulted in considerable cross-linking in the arterial wall mediated by the increased activation of transglutaminase 2 (TG2; a collagen cross-linking enzyme), lysyl oxidase, and advanced glycation end products (73). This cross-linking of collagen further compounds arterial stiffness. Of note, a decrease in NO promotes TG2 activation (74) and increases TGF-ß activation, which in turn increases TG2 expression and activation (73). Elastin breakdown also is a feature of arterial stiffness with obesity (75). Several matricellular proteins have been found to be important. Obesity increases TSP-1 expression in adipose tissue (61) and blood vessels (76). TSP-1 is a multifunctional antiangiogenic protein whose actions include potent activator of TGF-β, inhibition of NO synthesis via its CD36 and CD47 receptors, and inhibition of matrix metalloproteinases (MMPs). MMPs are implicated in the elastin breakdown and therefore play a crucial role in arterial remodeling by degrading components of the extracellular matrix. Increased oxidative stress can trigger MMP activity and changes in collagen and elastin deposition/resorption (77). Thus, obesity can lead to arterial stiffening via a variety of pathways, which can negatively affect the ability of the vessels to vasodilate.

PVAT-Induced Arterial Dysfunction

A current hypothesis is that PVAT plays a key role in arterial function, and that with obesity, PVAT undergoes pathological adaptations that induce arterial structural and functional changes. An exception to this is the cerebral network, which does not have any adipose tissue contained within the brain. However, the cerebrovasculature is negatively affected by obesity. It is thought that the excess WAT elicits a chronic low-grade inflammatory and oxidative state, which can have autocrine, paracrine, and endocrine effects, thus exerting their actions on the local and systemic arterial system, including the cerebrovasculature. Indeed, obesity enhances proinflammatory markers in the brain (78). However, more recently, research has focused on the adipose tissue that is in direct contact with the arterial system, specifically PVAT.

Various laboratories, including our own, have explored the role of PVAT-mediated arterial function. Using a wire myography chamber, we have shown that the EDD of the thoracic aorta (from lean healthy rat) cleaned of the surrounding thoracic PVAT (tPVAT) is improved when the healthy lean tPVAT conditioned media is administered into the myography chamber (4). However, maladaptive responses of tPVAT during obesity impair aortic EDD and induce arterial stiffness (4). For example, with obesity, the release of PVRF from PVAT is diminished, there is an increase in proinflammatory cytokines, and this toxic PVAT environment contributes to the arterial dysfunction (5). Indeed, the anticontractile properties of lean healthy PVAT are lost with obesity (4). Xia *et al.* (79) showed that endothelial nitric oxide synthase (eNOS) is expressed in PVAT, which aids in the production of NO, and that obesity leads to PVAT eNOS uncoupling. We have shown that the blunted aortic EDD in obese rats was further reduced in the presence of obese tPVAT due to reduce NO bioavailability (4). Of note, exposing a lean healthy aorta to the obese tPVAT significantly impaired EDD by ~25%, suggesting that factors in the obese tPVAT exert significant vasoactive actions. Conversely, exposing the unhealthy obese aorta with healthy lean tPVAT lowered reactive oxygen species (ROS) and improved NO production, which improved EDD in the obese aorta by ~20% (4). Our data suggest that the aortic endothelial dysfunction with tPVAT was due to obese tPVAT–derived TNF-α inducing aortic oxidative stress (4). As such, we acutely inhibited TNF-α by exposing the tPVAT to a TNF-α–neutralizing antibody, which restored aortic EDD in the presence of the tPVAT. We also have shown that inhibiting NADPH oxidase (NOX) 2 in obese tPVAT had the same impact as TNF-α neutralization antibody, suggesting tPVAT impairment of the aorta is dependent on oxidative stress. Additional pathways by which obese tPVAT may inhibit

aortic EDD NO production is through increased expression of caveolin-1, which negatively regulates eNOS via the interruption of calcium/calmodulin signaling (80). Another potential reason for the reduction in tPVAT-derived NO is due to a deficiency in PVAT adiponectin (4) that normally stimulates eNOS activity in PVAT adipocytes (81). Increased TNF-α inhibits adiponectin, removing its protective effects on tPVAT and aortic NO (81).

In addition to the aorta PVAT, during the early phase of diet-induced obesity, there is an adaptive overproduction of NO from mesenteric PVAT (17), whereas chronic exposure to diet-induced obesity leads to a reduction in mesenteric PVAT NO production and impaired EDD (18). Again, the increased oxidative environment within the PVAT seems to play a significant role, whereby incubation of the obese PVAT with antioxidant enzymes (superoxide dismutase and catalase) improved PVAT-intact mesenteric arterial function (18).

PVAT proteasome dysfunction also seems to play a role in the arterial dysfunction with obesity. Proteasomes are large protein complexes responsible for the proper regulation of proteins that control cell cycle progression and apoptosis. The proteasome consists of catalytic and regulatory subunits. The basic particle of the proteasome is the 20S core, which forms a gated channel through which a limited number of peptides and proteins enter (82). To alter the gate conformation and allow the degradation of a wider range of proteins (ubiquitinated, damaged and misfolded proteins), 19S regulatory complexes bind onto the 20S proteasome. The proteasome is able to recognize and degrade peptides and proteins to maintain equilibrium between normal protein production and degradation or to eliminate the damaged, misfolded/unfolded, or pathogenic proteins. Upon substrate recognition, 19S subunits are activated to unfold the substrate and facilitate its entrance through the gate and, finally, its route to the catalytic subunits (83). Oxidative stress is known to damage and misfold proteins, and the 20S complex of the proteasomes has a major role in recognizing and removing the damaged proteins. However, we have shown that obesity results in proteasome dysfunction in tPVAT, resulting in an accumulation of ubiquitinated proteins in the tPVAT (6). The increased accumulation of damaged and misfolded proteins can lead to further cellular and oxidative stress. Specifically, buildup of oxidized and ubiquitin products through activation of endoplasmic reticulum stress induced production of inflammatory cytokines (84), suggesting that proteasome dysfunction may contribute to the increased proinflammatory cytokine production in tPVAT. The importance of the proteasome is highlighted by its inhibition with MG132 in lean healthy tPVAT, blunting the beneficial actions of healthy tPVAT on aortic EDD (6).

In addition to functional changes, PVAT also seems to play a critical role in the development of arterial stiffness and remodeling. The Framingham Offspring and Third Generation cohorts showed that PVAT volume was associated with higher thoracic and abdominal aortic dimensions (85). Fleenor *et al.* (86) showed that oxidative stress within PVAT due to the aging process contributed to aortic stiffness in old mice. Aortic wall hypertrophy and adventitial collagen I accumulation were associated with greater superoxide production in PVAT, and inhibiting superoxide production with tempol reversed arterial wall hypertrophy and stiffness. In obese and aged mice, tPVAT was shown to increase arterial stiffness through alterations of oxidative status, leading to elastin fragmentation (87). To explore the role of tPVAT in aortic stiffness with obesity, we perform a coculture experiment in which a healthy aorta from a lean rat was exposed to either tPVAT from a lean or obese rat. The elastic modulus (a measure of arterial stiffness) of the lean rat aorta was not altered with the lean tPVAT; however, the lean aorta cultured with obese tPVAT showed an increased elastic modulus (4). tPVAT production of TNF-α may play an important role in the aortic stiffening. Indeed, the aortic stiffening in a lean rat in the presence of obese tPVAT was completely inhibited with a TNF-α–neutralizing antibody (4). TNF-α is known to stimulate the production of MMP9, and we found that obese tPVAT had increased MMP9 activity, which was associated with increased arterial stiffness. Inhibition of TNF-α by TNF-α–neutralizing antibody treatment also decreased MMP9 activity. Together, these data strongly suggest that dysfunctional PVAT plays a key role in the arterial dysfunction and remodeling associated with obesity.

EXERCISE TRAINING, ARTERIAL FUNCTION, AND PVAT

Regularly performed exercise induces structural and functional adaptations to large and small vessels. A meta-analysis of 17 studies revealed that exercise interventions significantly improved brachial flow–mediated dilation in overweight and obese adults (88). The repeated episodes of elevated blood flow and shear stress (mechanical stimulus) during exercise represent the primary physiological signal (integrins, ion channels, G protein–coupled receptors, and receptor tyrosine kinases) for endothelial structural and functional adaptations (89). The mechanisms of improved endothelial vasodilation after exercise training have been attributed to an increase in release of prostaglandin and NO bioavailability via an increase in eNOS expression and production of NO (90). Exercise also has been shown to reduce proinflammatory cytokines and oxidative stress molecules and improve anti-inflammatory cytokines (IL-4, IL-10, IL-13, etc.) (91). Indeed, we have shown that exercise training in obese rats leads to the classical arterial adaptive response whereby aortic oxidative stress was less and NO abundance was higher with improved aortic EDD (4). In addition to the aorta, we also have shown that other arterial regions (mesenteric and MCA) are improved with exercise training in obese rats (54). Furthermore, we have shown that aerobic exercise training in obese rats blunts the severity of the microcirculation rarefaction via an improved inflammatory profile (92). Despite the importance of exercise-induced shear stress on improving arterial function, arteries with a similar structure and exposed to similar hemodynamic forces display distinctly different arterial phenotypes. This would suggest that other additional local factors influence the regulation of arterial function and that tPVAT may be involved.

It is noted that PVAT phenotype is modified by continued weight lost, low-calorie diets, and bariatric surgery, which is linked to the beneficial arterial effects observed under these conditions (18). In addition, bariatric surgery reduced PVAT inflammation and restored the normal anticontractile PVAT phenotype in human small arteries (18). We have shown that 8 wk of treadmill running in OZRs increased tPVAT UCP-1 expression, suggesting a browner like phenotype (6). Similarly, exercise training increased UCP-1 content and reduced the size of the adipocyte in the mesenteric PVAT (19), suggesting a restoration of PVAT morphology. In addition, the improved

mesenteric PVAT phenotype limited the hypercontractile response of the mesenteric artery to serotonin (19).

We have shown that exercise training also lowered the tPVAT expression of immunoattractant cytokines (MCP-1 and CXCL1) and immune cell–specific markers (TNF-α, CD68, CD8) while limiting the reduction in anti-inflammatory cytokines (adiponectin, IL-10, IL-13, and IL-4) in OZR (6). These data suggest that exercise training reduced tPVAT inflammation, in part, by preventing the infiltration of T cells and macrophages. Similarly, exercise training for 16 wk in mice feed a high-fat diet reduced $CD11c^+$ inflammatory macrophages and $CD8^+$ T cells in epididymal adipose tissue, which was accompanied by a lower mRNA expression of TNF-α (93). Exercise also increases the secretion of adiponectin in obese tPVAT, which also may contribute to improved aortic EDD–mediated eNOS phosphorylation and production of NO in a caveolin-1–dependent manner. The reduced production of TNF-α and immune cells in the exercise-trained obese tPVAT likely exerts a couple of important actions on the autocrine signaling of tPVAT. First, lower TNF-α levels remove autocrine activation of oxidative stress from tPVAT, which can subsequently a) decrease the oxidative dissociation of the 19S from the proteasome, thereby improving proteasome function; b) decrease the sequestration of NO; and c) decrease inflammation-controlled gene expression. Indeed, proteasome function in the tPVAT was improved in the obese exercise-trained rat, which likely improved the recognition and breakdown of ubiquitinated proteins. Second, flipping the TNF-α–adiponectin balance toward adiponectin would promote the autocrine activation of enhanced NO abundance and phenotype maintenance. We also note an increase in GTP cyclohydrolase 1 expression, which is involved in the production of tetrahydrobiopterin, an essential cofactor for NO generation via eNOS (6) after exercise training in obese rat tPVAT. Furthermore, exercise training mitigated the expression of NOX2 in obese tPVAT, which was accompanied by a significant reduction in oxidative stress. The reduction in oxidative stress and limited eNOS uncoupling permitted improved NO bioavailability in the aorta and tPVAT and, as such, a corresponding improvement in aortic EDD with obesity (6).

We also have noted significant improvements in aortic stiffness after exercise training in OZR, which we believe are partly mediated through the improved tPVAT phenotype (reduced oxidative stress and MMP-9, improved NO, etc.) (6). Another study showed that exercise training for 17 wk prevented coronary PVAT advanced glycation end products (AGE) expression and secretion, as well as the increased arterial stiffness with reduction in elastin content and AGE accumulation in the presence of the PVAT conditioned medium from a heart failure swine model (32). In support of these data, inhibition of AGE with aminoguanidine prevented the detrimental impact of PVAT conditioned medium from the swine group on mouse aortic stiffness and wall remodeling (32). These results provide mechanistic evidence that chronic exercise training exerts its protective effect on pressure overload–induced coronary arterial stiffness mediated by a reduction in PVAT-related AGE secretion and associated oxidative stress and inflammation. The same study showed that exercise training attenuated the increases in coronary PVAT nitrotyrosine abundance, NF-κB p65 subunit expression, and IL-6/IL-8 secretion, indicating a potential integrative mechanism by which exercise prevents increased coronary arterial stiffness.

CONCLUSION

Obesity continues to be an epidemic with approximately 42.4% of Americans (2017–2018) presenting with obesity, and reports suggest that by 2030, nearly one in two adults (49%) will have obesity and one in four adults are projected to have severe obesity (1). Obesity results in various alterations to the macro- and microvascular structure and function that accelerate the risk for future CV events. Adipose tissues, through the release of adipokines, chemo/cytokines, hormones, and other currently unknown factors, impact, depending on the type of adipose tissue and its pathology, CV structure and function. The dysfunctional adipose tissues, due to obesity, are one of the major risk factors for CV disease. As PVAT is adjacent and integrated within the vessels, it is a major regulator of arterial physiology and pathophysiology. Indeed, PVAT may be considered a predictor of arterial disease and a therapeutic target. Obesity results in a phenotypic change to the PVAT manifested by reduced UCP-1 expression (reflecting a whiter-like adipose tissue composition) coupled with increased infiltration of T cell and monocyte/macrophage resulting in a pro-oxidative, proinflammatory, and reduced anti-inflammatory tPVAT environment. This obese PVAT phenotype results in arterial dysfunction, wall remodeling, and arterial stiffness (Fig. 1). Importantly, the obese PVAT phenotype is modifiable as evident with the beneficial changes noted with exercise training. This is reflected by an improved oxidative and inflammatory tPVAT environment with increased PVRF (including improved NO) and proteasome function. This improved tPVAT environment after exercise training results in improved aortic function and structure (Fig. 1). Therapeutically targeting tPVAT with exercise training or other therapeutics might accelerate the beneficial arterial adaptation and may provide a vital approach to reduce CV burden. However, more extensive and mechanistic research on the PVAT signaling pathways and its cross-talk with the various arterial components (EC, VSMC, fibroblasts, etc.) is needed to further understand the physiological and pathological roles of PVAT.

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