The role of perivascular adipose tissue in vasoconstriction, arterial stiffness, and aneurysm

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Abstract

Since the "rediscovery" of brown adipose tissue in adult humans, significant scientific efforts are being pursued to identify the molecular mechanisms to promote a phenotypic change of white adipocytes into brown-like cells, a process called "browning". It is well documented that white adipose tissue (WAT) mass and factors released from WAT influence the vascular function and positively correlate with cardiac arrest, stroke, and other cardiovascular complications. Similar to other fat depots, perivascular adipose tissue (PVAT) is an active endocrine organ and anatomically surrounds vessels. Both brown-like and white-like PVAT secrete various adipokines, cytokines, and growth factors that either prevent or promote the development of cardiovascular diseases (CVDs) depending on the relative abundance of each type and their bioactivity in the neighboring vasculature. Notably, pathophysiological conditions, such as obesity, hypertension, or diabetes, induce the imbalance of PVAT-derived vasoactive products that promote the infiltration of inflammatory cells. This then triggers derangements in vascular smooth muscle cells and endothelial cell dysfunction, resulting in the development of vascular diseases. In this review, we discuss the recent advances on the contribution of PVAT in CVDs. Specifically, we summarize the current proposed roles of PVAT in relationship with vascular contractility, endothelial dysfunction, neointimal formation, arterial stiffness, and aneurysm.

Keywords

aneurysm; arterial stiffness; endothelial dysfunction; perivascular adipose tissue; vascular calcification

Introduction

The majority of adipose tissues in the body is white adipose tissue (WAT). WAT is mainly involved in energy storage and mobilization. Excess fat accumulation in WAT, particularly

in visceral WAT in the abdomen, is highly associated with metabolic diseases such as type 2 diabetes and cardiovascular complications [1, 2]. Coexisting with WAT, brown adipose tissue (BAT) is specialized in energy expenditure. Due to the thermogenic properties of BAT, its presence in certain anatomical locations in adult humans suggests a beneficial role in preventing the development of metabolic diseases [3]. Targeting the "browning" of WAT have recently been reported to transform the energy storage capability of WAT to BAT-like energy expenditure characteristics [4]. Adipocytes with browning ability in WAT are so-called brite or beige adipocytes, having characteristics of adipocytes in classic BAT [5, 6]. The molecular signature of active adipocytes is the matter of active research investigation. From current knowledge, adipocytes from the supraclavicular area in humans display an intermediate gene expression profile characteristic of brown and brite adipocytes [7].

Although there is a concept of "good" brown or beige fat in the body and "bad" fat characteristics of WAT in obese and obesity-related complications, WAT is required for maintaining human homeostasis. For instance, patients with lipodystrophy suffer from hypertension, severe insulin resistance, and other complications typically seen in obese patients [8]. These phenotypes have also been observed in several mouse models lacking both WAT and BAT [9–12]. Additionally, different types of adipose tissue exhibit distinct morphology and biology, and this diversity is true in adipose tissues found in different anatomical locations. Experimental and clinical studies show that dysfunctional visceral WAT is positively related to cardiovascular risk [2], whereas resident beige adipocytes in subcutaneous WAT [5] are negatively correlated with cardiovascular risk. This may be partially due to beige's high capability of energy expenditure [13]. Although it is beyond the scope of this review to discuss the roles of obesity and/or lipodystrophy, or different adipose tissue in metabolic diseases, it is worthwhile to note that adipokines and/or cytokines released from adipocytes into the circulation are responsible for the crosstalk between adipose tissue and long-distance target organs (e.g., liver, skeletal muscle, kidney, heart, and vasculatures). Furthermore, small amounts of adipose tissues are directly attached to organs that are susceptible to metabolic diseases [14].

Recent studies show that pararenal, pericardial, and perivascular adipose tissue (PVAT) are highly related to cardiovascular diseases (CVDs) [15]. PVAT is a special depot of adipose tissue that adjacently surrounds blood vessels. Although similar in action to other adipose tissue depots by acting as a support tissue for protecting vessels against neighboring tissues, PVAT is also an endocrine organ that releases a wide range of biologically active molecules that may have profound influence in the vasculature [16]. Paracrine vasoactive effects and their underlying mechanisms of PVAT-derived factors in vasculature physiology and pathophysiology have been intensively studied. In fact, serial reviews have already summarized the relationships between PVAT and established CVDs such as atherosclerosis and hypertension [17–23]. Here we focus on the newest results on the roles of PVAT on vasoconstriction, endothelial dysfunction, vascular calcification, arterial stiffness, and aneurysm (Figure 1).

Diversity of PVAT

Most blood vessels, including small vessels in organs, are surrounded by PVAT [24]. Similar to different types of adipose tissue in different depots, PVAT shows divergent types according to anatomical locations [18]. The major blood vessels widely studied and that relate to CVDs are the mesenteric artery, coronary artery, carotid artery, femoral artery, and large conduit aorta. In mice, which are broadly used for experimental studies, thoracic PVAT displays characteristics of the BAT phenotype, with high vascularization and multiple small lipid droplets and numerous mitochondria in adipocytes [25]. Abdominal PVAT displays an intermediate phenotype between WAT and BAT [26], whereas mesenteric, carotid, and femoral PVAT is by a WAT phenotype. No PVAT is found in the coronary arteries of mice [18]. A similar phenotypic pattern of PVAT is observable in rats [27]. Compared with thoracic PVAT, abdominal PVAT is more prone to inflammation, as indicated by more markers of immune cell infiltration and greater expression of inflammatory genes in abdominal PVAT than for those in thoracic PVAT [27]. In addition, histological analysis indicates a structural similarity between thoracic PVAT and BAT and between abdominal PVAT and visceral WAT [27].

Christine et al. reported distinct phenotypic signatures between human perivascular (peritibial or popliteal arteries) and subcutaneous adipose tissues in patients undergoing below- and above-knee amputations (for unreconstructable chronic critical limb ischemia or an unsalvageable foot). Compared to peritibial or popliteal PVAT, subcutaneous adipose tissue exhibits more of a proinflammatory phenotype. Interestingly, age was positively correlated with plasminogen activator inhibitor-1 expression in PVAT, whereas hyperlipidemia was negatively correlated with PVAT adiponectin [28]. Consistently, the metabolic activity of PVAT varies remarkably depending on the anatomical location. Using liquid chromatography-tandem mass spectrometry-based metabolic lipidomic analysis, Claria et al. demonstrated that PVAT (surrounding popliteal, anterior tibial, posterior tibial, and peroneal arteries) collected from patients undergoing major lower extremity amputation displays higher levels of specialized proresolving mediators, including resolvins and lipoxins, than those in subcutaneous adipose tissue [29]. These findings indicated that the distribution of bioactive lipid mediators is highly dependent on the localization of human fat depots and uncovers a specific pattern of specialized proresolving mediators closely associated with peripheral artery diseases.

Genome-wide expression analyses identified differentially expressed genes between adipocytes derived from human subcutaneous adipose tissue collected from the upper abdomen subcutaneous region and PVAT collected from the left coronary artery. About 37.8% of up-regulated genes in PVAT were associated with angiogenesis, vascular biology, or inflammation (including *TNFRSF11B*, *PLAT*, *TGFB1*, *THBS2*, *HIF1A*, *GATA6*, and *SERPINE1*), whereas down-regulated genes are associated with vascular biology and inflammation (including *ANGPT1*, *ANGPTL1*, and *VEGFC*). Consistent with the emergent hypothesis that adipocytes in PVAT differentially regulate angiogenesis and inflammation, cell culture-derived adipocyte-conditioned media from PVAT strongly enhanced endothelial cell tubulogenesis and monocyte migration compared with media obtained from subcutaneous adipocytes. These findings demonstrate that PVAT mediates vascular

inflammatory crosstalk in atherosclerosis by being able to signal both endothelial and inflammatory cells [30]. However, it is notable that the human specimens used in all these studies were collected from patients with disease conditions. It is unclear whether those disease conditions contributed to the inflammation in PVAT other than in subcutaneous adipose tissue.

PVAT constricts vessels

Vascular reactivity in the vascular chamber is a well-established method to assess the contribution of PVAT to the regulation of the vascular tone. Using isometric conditions of the vessel of choice under conditions in which the adjacent PVAT is preserved or in vessels void of PVAT but incubated with conditioned media derived from PVAT have led to the identification of several anticontractile factors and vasodilators in the PVAT (Figure 2A). These include adiponectin [31], hydrogen sulfide [32], angiotensin 1–7 [33], methyl palmitate [34], or prostacyclin [25], among others. Thus, the majority of literature suggests that the "anticontractility" mediated by PVAT-derived vasodilators is the major characteristic of PVAT vasoactivity [35, 36]. Studies have demonstrated that the anticontractile effects of PVAT are mediated through the activation of potassium channels [37]. In the past 2 years, the anticontractile effects of human PVAT in different anatomical locations have been reported. The pharmacological blockage of potassium channels on human internal thoracic arteries further suggests that human PVAT releases relaxing factors. Ca^{2+}-dependent potassium channels might be involved in its anticontractile effects [38]. PVAT-derived prostaglandin E2 (PGE2) and prostacyclin in the saphenous vein region attenuated the vessel contractile response to noradrenaline. Interestingly, pretreating the vessels with a cyclooxygenase (COX) inhibitor increased noradrenaline-induced contraction in the saphenous vein but not in the internal mammary artery with PVAT. This is consistent with the fact that PGE2 in the PVAT surrounding internal mammary artery is lower than in the PVAT surrounding the saphenous vein. This suggests that the mechanisms underlying the anticontractile effects of PVAT vary in anatomical locations [39]. Similar to observations in mice and rats, the anticontractile effects of human PVAT in the subcutaneous small artery regions were lost in obese patients and were restored 6 months after bariatric surgery. Local oxidative stress and inflammation may contribute to the impaired anticontractile effects of PVAT in obese subjects. Catalase and superoxide dismutase could rescue the anticontractile effects of obese PVAT. In addition, an improvement in anticontractile effects after bariatric surgery was accompanied by reduced macrophage infiltration and increased PVAT adiponectin [40]. Additional literature in the past 2 years illustrated the mechanisms of PVAT anticontractility.

Withers et al. reported that cGMP-dependent protein kinase (PKG) associates with adipocyte adiponectin expression. PKG activation failed to restore the absent PVAT anticontractility in arteries from adiponectin$^{-/-}$ mice. The anticontractile effects of PVAT were not present in arteries from PKG$^{-/-}$ or inhibition of PKG signaling in wild-type mice, suggesting that PKG plays a role in regulating PVAT-mediated anticontractility [41]. Large-conductance Ca^{2+}-activated K^+ (BKCa) channels may contribute to the anticontractile effects of PVAT as well [42]. The anticontractile effects of PVAT were not observed in the

mesenteric artery isolated from BKCa$^{-/-}$ mice. In addition, PVAT from BKCa$^{-/-}$ mice did not elicit anticontractile responses in wild-type arteries [31].

On the other hand, recent studies show that PVAT significantly constricts vascular smooth muscle by a variety of PVAT-derived contracting factors (PDCFs). The identities of PDCFs remain to be elucidated but were identified when preincubating the vessels from PVAT directly in the organ bath (Figure 2B). When we investigated the roles of mouse thoracic PVAT on endothelial function, substances in PVAT unexpectedly initiated the contraction of vessel rings, if adding minced PVAT mixtures into the wire myograph chambers mounted with vessel rings without PVAT [25] (Figure 2B). Adrenaline and prostaglandin released from PVAT contribute to vessel contraction as evidenced by the preincubation of vessel rings with a COX inhibitor or α-adrenergic receptor antagonists blocked by PVAT-induced vasocontraction [43]. Indeed, the sympathetic nervous system and its neurotransmitter effectors are undeniably important to blood pressure control [44]. Recently, Ayala-Lopez et al. also demonstrated that PVAT in normal rat thoracic aortas and superior mesenteric arteries contains significant concentrations of catecholamines. Importantly, PVAT components can release noradrenaline to constrict vessel rings independent of sympathetic nerves as evidenced by the removal of the celiac ganglion as a neuronal source of catecholamines for superior mesenteric artery. PVAT did not significantly reduce tyramine-induced vessel contraction [45]. Further studies showed that PVAT obtained from obese mice potentiates vessel contractility in response to serotonin and phenylephrine in a COX-dependent manner [46]. Consistent with these findings, PVAT from both healthy rats and rats with metabolic syndrome revealed COX-2 activity. Immunoassay confirmed the release of PGE2, thromboxane A2, and prostacyclin from PVAT [47]. Additionally, Owen et al. examined the mechanisms underlying the influence of coronary PVAT-derived factors from lean versus obese swine on vasomotor tone of coronary arteries from Ossabaw swine. Results showed that coronary PVAT increased baseline tension and potentiated the contraction of isolated arteries to prostaglandin F2 α (PGF2 α) in proportion to the amount of PVAT present. The inhibition of Cav1.2 channels abolished the coronary PVAT-augmented contractile effects of vessels in response to KCl. Furthermore, H_2O_2-mediated vasodilation was diminished by coronary PVAT. Further studies revealed that inhibition of Rho kinase significantly blunted artery contractions to PVAT. Thus, Rho-dependent signaling and K^+ and $Ca_{V1.2}$ channels may contribute to the contractile effects of PVAT [48]. In addition, unknown factor(s) released from PVAT might induce vessel contraction via the inhibition of endothelial nitric oxide (NO) and increase of the caveolin-1 (Cav-1) protein. Aortic NO production was diminished, whereas Cav-1 protein expression was significantly increased in aortas after PVAT treatment. The depletion of caveolae by methyl-β-cyclodextrin abolished the effects of PVAT on the enhancement of vasoconstriction and reversed the impairment of aortic NO production [49]. Interestingly, chemerin is a peptide that is abundantly expressed in PVAT and contracts isolated rat thoracic aortas, superior mesenteric arteries, and mesenteric resistance arteries. Watts et al. further demonstrated that ChemR23, the primary receptor of chemerin, is expressed in both the endothelial and medial arterial layers. The blockage of ChemR23 by CCX832 significantly reduced phenylephrine- or PGF2 α-induced vasoconstriction, suggesting that chemerin contributes to contraction

[50]. Taken together, PVAT-derived catecholamines and prostaglandins modulate arterial vasoconstriction via their receptors in vascular smooth muscle cells (VSMCs).

PVAT modulates endothelial function

As discussed above, PVAT modulates vasoactivity in both contractile and anticontractile manner. Nevertheless, PVAT-derived factors such as adipokines, cytokines, and growth factors may directly target endothelial smooth muscle cells and VSMCs (modulating vasculature function). Indeed, aortic rings (with or without PVAT) isolated from endotoxemic rats showed lower contractile effects in response to phenylephrine. Transferring bathing solution incubated with PVAT from endotoxemic rats potentiated PVAT-induced relaxation in the recipient vessel rings. The mechanisms are unclear, but the levels of inducible NO synthase (iNOS) protein and mRNA in endotoxemic PVAT were significantly higher than those in the control PVAT [51]. Additionally, inflammation and oxidative stress in obese PVAT might modulate endothelial function. The mesenteric fat mass was significantly increased in mice fed a high-fat diet for 32 weeks associated with impaired mesenteric endothelial-dependent relaxation in the presence of PVAT. It was unclear whether high-fat diet-induced PVAT dysfunction leads to endothelial dysfunction or vice versa because NO bioavailability was reduced in the mesenteric artery of mice fed a high-fat diet. However, superoxide levels were higher, and superoxide dismutase activity was reduced in the PVAT of these obese mice [52]. Feeding of a high-fat diet for 6 weeks also greatly induced endothelial dysfunction and enhanced macrophage infiltration in PVAT in the carotid artery region of rabbits. C-reactive protein treatment further promoted macrophage infiltration in PVAT and aggravated endothelial dysfunction, especially in PVAT-present arteries [53]. Consistently, obese humans showed intravascular superoxide excess and a higher expression of vascular/perivascular inflammatory cytokines [e.g., tumor necrosis factor-α (TNF-α)]. Removing PVAT from small arteries isolated from obese humans reversed the endothelial dysfunction [54]. Antioxidative treatment of ovariectomized rats with Tempol prevented endothelial dysfunction and restored the enhancing effects of PVAT on acetylcholine-induced mesenteric artery relaxation [55]. The systemic knockout of adipose triglyceride lipase (ATGL) in mice was characterized by an increasing PVAT mass surrounding the thoracic aorta. These mice suffer from pronounced endothelial dysfunction associated with reduced NOS expression and activity in endothelial cells. Interestingly, the smooth muscle cell layer maintained functional integrity despite the inflammation in PVAT of ATGL knockout mice [56]. A high-fat diet also resulted in down-regulated expression of rictor in mouse thoracic PVAT. Rictor, an essential component of mammalian target of rapamycin complex 2 (mTORC2), is related to inflammation. Adipose tissue specifically deleted of rictor showed an increase in gene expression and release of proteins, TNF-α, MCP-1, and interleukin-6 (IL-6) in PVAT. Rictor deficiency also reduced the phosphorylation of the mTORC2 downstream target Akt at Ser^{473} in PVAT but was unaffected in the aorta. Interestingly, isolated thoracic aorta rings from rictor-deficient mice exhibited increased contraction and impaired relaxation. However, the expression of iNOS was up-regulated without affecting macrophage infiltration in PVAT from rictor-deficient mice [57].

Inflammatory PVAT contributes to neointimal formation

A causal relationship between disturbed lipid metabolism in PVAT and endothelial dysfunction remains elusive. In addition to affecting endothelial function, PVAT-derived factors may contribute to the development of neointimal formation after intravascular injury. Manka et al. transplanted thoracic PVAT from donor mice fed a high-fat diet to the carotid arteries of recipient low-density lipoprotein receptor knockout mice also fed a high-fat diet. Wire injury was performed 2 weeks after transplantation. Transplantation of thoracic PVAT accelerated neointimal hyperplasia, adventitial angiogenesis, and macrophage infiltration. This phenotype might be related to the inflammatory response in the injury region. Transplantation of PVAT from MCP-1-deficient mice substantially attenuated adventitial angiogenesis and neointimal formation but not adventitial macrophage infiltration [19].

Neointimal formation also results from inflammation in association with proliferation of VSMCs. Four weeks of TNF-α injection significantly increased intima-media thickening of the mouse abdominal aorta. This was associated with increased matrix metalloproteinase-2 (MMP-2), MCP-1, neutrophils, CD3, and CD68 in abdominal PVAT. PVAT homogenates from TNF-α-injected mice significantly increased cultured VSMC proliferation in vitro, with associated up-regulated transforming growth factor-β 1 (TGF-β 1). Cotreatment of VSMCs with TGF-β 1 inhibitor attenuated inflammatory PVAT-induced cell proliferation, suggesting that chronic inflammation in PVAT potentiated TGF-β 1-mediated VSMC proliferation [58]. Additionally, PVAT-derived proinflammatory adipokines, such as leptin, might contribute to neointimal formation. This is evidenced by adenoviral-mediated overexpression of leptin in the perivascular region, which promoted neointimal formation in wild-type mice but not in leptin receptordeficient mice. In addition, transplantation of visceral fat from diet-induced obese wild-type mice in the pericarotid artery region of immunodeficient mice enhanced neointimal formation without affecting the systemic leptin levels. Yet, pericarotid artery transplantation of visceral fat of *ob/ob* mice did not promote neointimal formation [59].

Another example of PVAT-derived proinflammatory factor is angiopoietin-like protein 2 (Angptl2), which promotes inflammation in obese adipose tissue. PVAT Angptl2 was significantly induced by aging and hypercholesterolemia. Similar to leptin, transplantation of PVAT from adipose tissue specific to Angptl2 transgenic mice accelerated neointimal formation after endovascular injury, whereas transplantation of PVAT from Angptl2-deficient mice attenuated vascular inflammation and neointimal hyperplasia [60]. Therefore, inflammatory PVAT tends to enhance the development of neointimal hyperplasia. Aging and obesity might enhance inflammation and oxidative stress in organs. In addition, obesity-induced oxidative stress and inflammation in PVAT were exacerbated by aging and significantly increased macrophage infiltration. The PVAT of aged, obese mice significantly promoted proinflammatory phenotypic alteration in the vascular wall of young mice [61].

PVAT in vascular calcification

Vascular calcification is a process with deposition of ectopic minerals in the vascular wall. Ectopic calcification is not only a phenomenon as a passive consequence of aging but also a

tightly regulated process that involves competition between inhibition of mineralization and promotion of calcification. Vascular calcification typically occurs in the medial layer of the vessel and in neointimal plaques in atherosclerotic vessels [62]. Vascular calcification occurs frequently in concert and contributes synergistically to CVDs; it is positively correlated with risk for any cardiovascular event [63]. During the development of vascular calcification, VSMCs in the vascular wall appear to switch from a normal contractile phenotype to an osteochondrogenic phenotype. Some hypotheses argue that cells with an osteochondrogenic phenotype might originate from pericytes or circulating mesenchymal precursors. Mineralization will occur within the extracellular matrix once these osteochondrogenic cells are established. The mechanisms underlying vascular calcification remain under investigation. New discoveries related to extracellular vesicles, microRNAs, and calciprotein particles continue to reveal the mechanisms that are involved in the initiation and progression of vascular calcification [64]. From the clinical perspective, thoracic PVAT has been associated with abdominal aortic and coronary calcification [65]. More recently, a clinical study suggested that PVAT might be involved in the development of vascular calcification. Women with systemic lupus erythematosus (SLE) had greater median thoracic aortic PVAT and greater aortic calcification than healthy women. Total aortic PVAT volumes remained markedly associated with SLE after adjusting for circulating inflammatory markers [66]. In addition, after adjusting for sex, age, and other measures of adiposity in a cross-sectional study in 100 HIV-infected adults, thoracic PVAT mass was independently associated with coronary artery calcification [67]. However, these studies do not infer causality regarding the relationship between PVAT volume and vascular calcification. Further investigations are needed to determine the contribution of PVAT-derived factors on the phenotypic switch of VSMCs from a contractile to an osteochondrogenic phenotype or other mechanisms that relate to vascular mineralization.

PVAT and arterial stiffness

Arterial stiffness is an inevitable consequence of the vascular aging process in humans. Studies show a close relationship between arterial stiffness and microvascular damage in the heart, brain, and kidney. Such changes may occur early in the course of diseases associated with premature vascular aging. Therefore, arterial stiffness is a key determinant and in particular can be considered as a measure of the cumulative influence of cardiovascular risk factors due to aging on the arterial tree. Measuring arterial stiffness could prevent patients from being mistakenly classified as at low or moderate risk. In addition, therapies or strategies that directly alter the compliance of the vessel wall may be more effective because they would halt the negative feedback cycle of stiff vessels increasing the load on the heart.

It is well accepted that obesity is associated with increased CVDs. Obese subjects exhibit increased arterial stiffness compared with nonobese subjects, and weight loss improves arterial compliance [68]. A recent population study showed that skin-fold thickness could be a predictor of arterial stiffness in hypertensive patients, indicating that obesity is linked to higher stiffness [69]. Importantly, concomitant with the expansion of adipose tissue, PVAT mass is increased in obese conditions. However, it is unclear whether arterial stiffness in obese subjects is owing to PVAT expansion. The Framingham Offspring and Third Generation cohorts showed that PVAT volume was associated with higher thoracic and

abdominal aortic dimensions and persisted after adjusting for age, sex, and cardiovascular risk factors including body mass index (BMI) and visceral adipose tissue volume [70]. This strongly supports the notion that human PVAT contributes to the development of vascular diseases [71]. However, our knowledge of the relationship between PVAT and arterial stiffness is limited. Studies assessing vascular mechanics have been performed under the assumption of uniform thickness of the vessel wall without consideration of its surrounding PVAT. Liu et al. quantified the radial constraint of the surrounding tissue for carotid and femoral arteries. Consequently, removing the surrounding tissue results in a significant increase of the circumferential wall strain and stress compared to the intact state [72]. Using geometrical measurements of pig aortas and histological samples to construct analyses models, Kim et al. confirmed that the aorta model with surrounding PVAT resulted in a comparatively uniform stress level within the aortic media under the in vivo pressure range. In addition, this study shows that stress in the vascular wall can be altered directly by changes in the stiffness of the surrounding tissues [73].

Recently, owing to the fact that an activation of the vascular renin-angiotensin-aldosterone system (RAAS) is seen in human and animal models of obesity and diabetes and associated with enhanced oxidative stress and inflammation in vascular tissue, and the fact that the majority of RAAS is in PVAT but not in the medial layer of vasculature, it is suspected that local RAAS in PVAT is an important element involved in arterial stiffness [74]. Fleenor et al. demonstrated that superoxide signaling within PVAT contributes to arterial stiffness in old mice, which had greater large artery stiffness accompanied with greater production of superoxide and inflammatory proteins in aortic PVAT. Arterial wall hypertrophy and adventitial collagen I was associated with greater superoxide production in PVAT. Treating old mice with Tempol, a superoxide scavenger, reversed arterial wall hypertrophy and stiffness [75]. Consistently, the aortas of *ob/ob* mice were surrounded by an extremely large amount of PVAT mass and had increased arterial stiffness. The aortas of *ob/ob* mice exhibited decreased lysyl oxidase activity and cross-linked elastin and increased elastin fragmentation and elastolytic activity, which were associated with inflammation. The inhibition of lysyl oxidase significantly increased arterial stiffness in lean mice as well. In addition, serum lysyl oxidase levels were lower in obese humans and associated with stiffer arteries [76]. Quantifying analyses of thoracic PVAT and visceral fat in the Framingham Heart Study participants using multidetector computed tomography showed that mean thoracic PVAT and visceral fat were 13.2 and 1763 cm^3, respectively. After BMI adjustment, thoracic PVAT and visceral fat are associated with large artery stiffness, supporting the hypothesis of associations between PVAT and arterial stiffness [77].

PVAT in aneurysm development

Aneurysm is a complex vascular connective tissue disorder, as this disease is a result of the complete destruction and/or degradation of extracellular matrix proteins in the aortic wall. PVAT plays a critical role in the recruitment of immune cells into the adventitia layer of the vascular wall. T cells and macrophage infiltration in PVAT has been observed in experimental models of hypertension including angiotensin II (Ang II) or endothelin-1 preceding observable pathological vascular dysfunction such as atherosclerosis, arterial stiffness, or aneurysm [78, 79]. Upon the development of hypertension, significant changes

of adipokine expression profile are observed in the PVAT. Furthermore, inflammatory cytokines in these experimental models are profoundly increased in PVAT, with virtually no alteration in WAT. PVAT is the preferential tissue of T-cell recruitment and homing, as it express CC chemokine receptors during the development of Ang II hypertension [80]. Inflammatory signaling in the vascular wall might contribute to aneurysmal development. However, at present, antihypertensive therapy is the only standard treatment for aortic aneurysm. Using an Ang II and β-aminopropionitrile-induced novel aneurysm model in 7-week-old C57BL/6J male mice, Kurobe et al. demonstrated that the administration of Eplerenone, a selective mineralocorticoid receptor antagonist, significantly reduced aneurysmal development. Notably, the expression of TNF-α, IL-6, and MMP-2 were decreased in both the aortic wall and PVAT of mice treated with Eplerenone. Eplerenone markedly inhibited macrophage infiltration in the aortic wall and PVAT [81]. It is unclear whether PVAT inflammation in this novel aneurysm model is a consequence or cause of aneurysmal development. However, it is accepted that adventitial recruitment of macrophage precursors plays critical roles in aneurysmal development. Macrophages in aortic adventitia were F4/80$^-$ and CD14^{hi}. Significantly, patients with an abdominal aortic aneurysm showed increased CD14 in the aorta, whereas CD14-deficient mice were resistant to aneurysmal formation. In addition, IL-6 potentiated the up-regulation of CD14 expression and CD14-dependent chemotaxis in human THP-1 monocytes treated with conditioned medium from PVAT, suggesting that PVAT-derived proinflammatory factors might promote active macrophage infiltration to induce aneurysmal development [78]. These results support the observation that higher thoracic and abdominal aortic dimensions were associated with PVAT volume in the Framingham Offspring and Third Generation cohorts [70].

Outlook

The inflammatory characteristics of PVAT in specialized experimental conditions such as intravascular injury, obesity and insulin resistance, and hypertension lead to the hypothesis that PVAT is bad for health. In fact, we are not able to distinguish that inflammatory PVAT is the consequence of CVDs or inflammatory PVAT leads to CVDs. Indeed, similar to adipose tissues in other depots, PVAT mass is greater in the conditions of obesity, leading to T-cell and monocyte/macrophage infiltration and adipocyte dysfunction. However, metabolic consequences and cardiovascular outcomes might be completely different depending on the size of adipocytes in PVAT. Dysfunctional hypertrophic PVAT contributes to the development of CVDs via the alterations of the autocrine/paracrine profile in PVAT, which disrupt the balance of proinflammatory and anti-inflammatory phenotype as well as the contractile and anticontractile characteristics in PVAT. However, functional PVAT is required to maintain vascular homeostasis. Due to distinct phenotypic PVAT in different anatomical locations and different species, we should carefully interpret the roles of PVAT in the development of relevant CVDs. In addition, PVAT shares common pathology with fat tissues in other depots such as subcutaneous, gonadal, and visceral regions; therefore posing a challenge to elucidate the overall effects of PVAT as distinct from other fat tissues regarding contributions to the outcomes of CVDs.

Investigations on PVAT and its roles in physiology and pathophysiology on the surrounding vascular wall are booming now. A consideration on the phenotypic changes of PVAT under disease conditions cannot be ignored from those of the vasculature. PVAT shares equal importance as endothelial, medial, and adventitial layers for maintaining vascular homeostasis. In the ensuing years, high-throughput analytical methods, including proteomics and deep sequencing analysis, will reveal novel PVAT-derived cytokines, chemokines, as well as proinflammatory and anti-inflammatory factors. Employing these methods will allow for the discovery of the relevant receptors and signaling pathways of these PVAT-derived factors in the cells of endothelial, medial, and adventitial layers.

Acknowledgments

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Highlights

PVAT has divergent characteristics in different anatomical locations and different species.

PVAT secretes anticontractile, anti-inflammatory, and antioxidative stress factors and regulates the vascular tone.

A dysfunctional PVAT precedes observable vascular changes under disease conditions and is associated with endothelial dysfunction, arterial stiffness, and vascular calcification—the risk factors for CVDs.
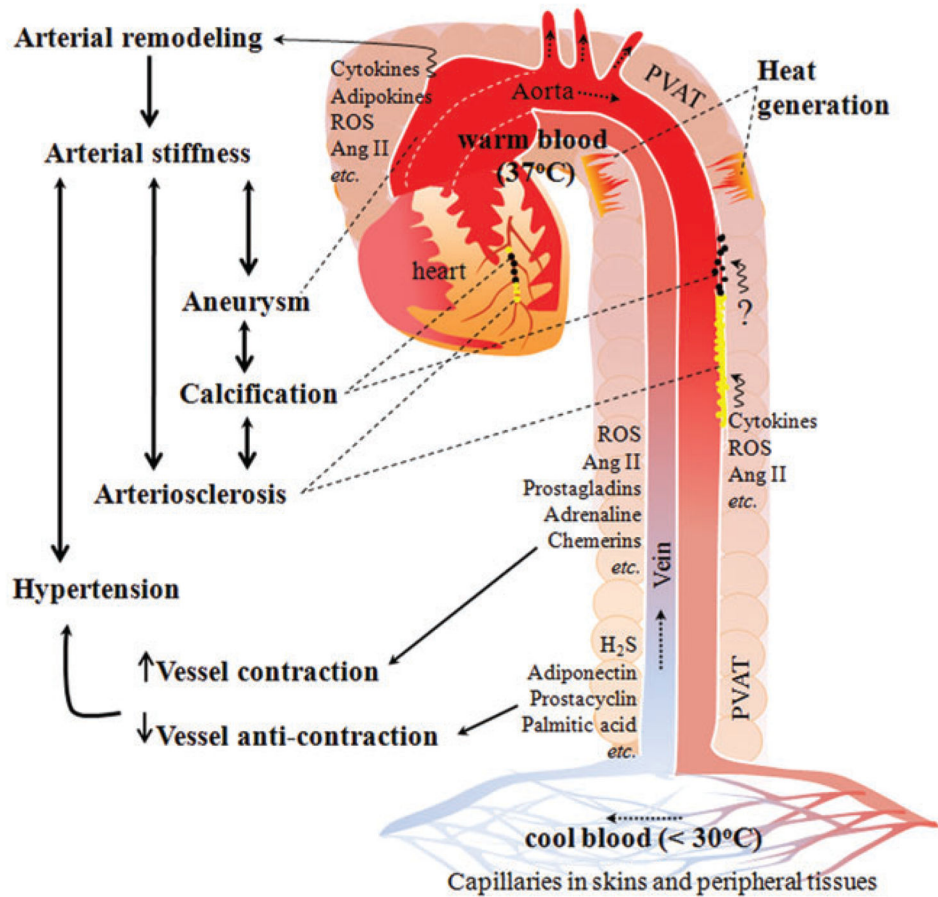
Figure 1.
Relationship between PVAT and cardiovascular risks. Thermogenesis in functional brown-like PVAT is one of the required players to maintain blood temperature in veins from peripheral tissues. A circulating blood temperature gradient exist between the blood leaving the heart (37°C in the left ventricle) and the peripheral blood including the capillaries at the skin (~28°C in skin surface), and it is restored to 37°C when the blood returns to heart from veins. Of equal importance, cytokines, adipokines, and other factors released from dysfunctional PVAT contribute to arterial remodeling and endothelial dysfunction. In addition, dysfunctional PVAT-derived factors promote calcification in the arterial wall, which will accelerate the development of arterial stiffness and arteriosclerosis. Additionally, dysfunctional PVAT release contractile factors such as prostaglandins, Ang II, chemerin, and adrenalin to enhance vascular contractility, whereas the loss of PVAT-derived anticontractile factors such as prostacyclin and adiponectin reduce the anticontractile ability of PVAT, leading to arterial stiffness, hypertension, and the development of vascular lesion formation, vascular calcification, or aneurysmal formation. Dashed arrows indicate the direction of bloodstream.
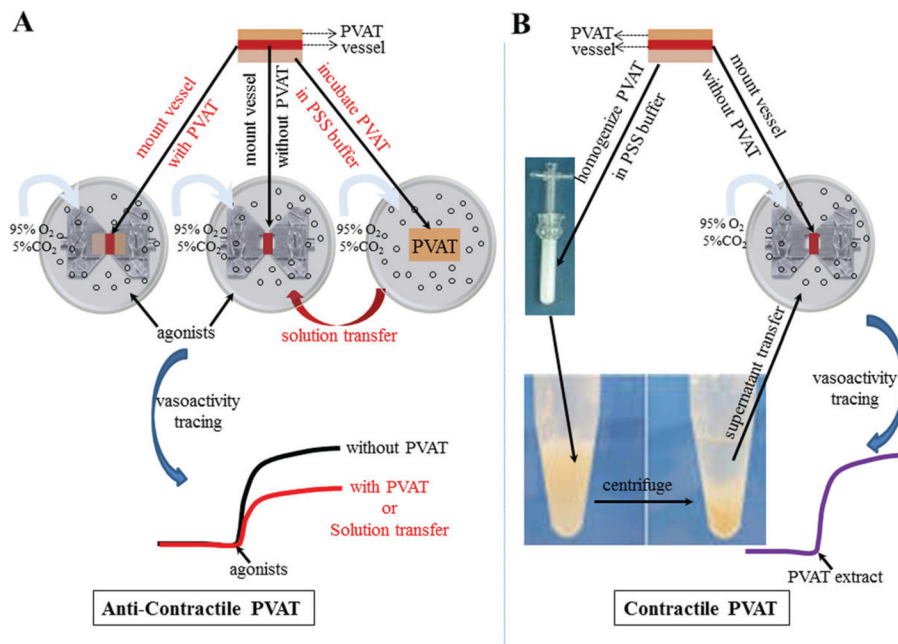
Figure 2.
Common experimental protocols leading to the identification of vasoactive substances in PVAT.
(A) Anticontractile PVAT. Under isometric conditions on vessels either mounted with an intact surrounded PVAT or in PVAT-less vessels preincubated with conditioned media from PVAT is removed, vasoconstriction responses are reduced in response to agonists such as epinephrine and norepinephrine. (B) Contractile PVAT. On the other hand, PVAT crude extracts or direct incubation of PVAT is able to constrict vessels mounted into the myograph chamber revealing the existence of PVAT-derived vasoconstrictors.