Cardiovascular Diabetology

REVIEW

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Perivascular adipose tissue: a central player in the triad of diabetes, obesity, and cardiovascular health

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Abstract

Perivascular adipose tissue (PVAT) is a dynamic tissue that affects vascular function and cardiovascular health. The connection between PVAT, the immune system, obesity, and vascular disease is complex and plays a pivotal role in the pathogenesis of vascular diseases such as atherosclerosis, hypertension, and vascular inflammation. In cardiometabolic diseases, PVAT becomes a significant source of proflammatory adipokines, leading to increased infiltration of immune cells, in cardiometabolic diseases, PVAT becomes a significant source of proinflammatory adipokines, leading to increased infiltration of immune cells, promoting vascular smooth muscle cell proliferation and migrationpromoting vascular smooth muscle cell proliferation and migration. This exacerbates vascular dysfunction by impairing endothelial cell function and promoting endothelial activation. Dysregulated PVAT also contributes to hemodynamic alterations and hypertension through enhanced sympathetic nervous system activity and impaired vasodilatory capacity of PVAT-derived factors. Therapeutic interventions targeting key components of this interaction, such as modulating PVAT inflammation, restoring adipokine balance, and attenuating immune cell activation, hold promise for mitigating obesity-related vascular complications. Lifestyle interventions, pharmacological agents targeting inflammatory pathways, and surgical approaches aimed at reducing PVAT mass or improving adipose tissue function are potential therapeutic avenues for managing vascular diseases associated with obesity and PVAT dysfunction.

Keywords Cardiovascular disease, Type 2 diabetes, Obesity, Inflammation, Perivascular adipose tissue, Therapeutic interventions

Introduction

Perivascular Adipose Tissue (PVAT) is a metabolically active tissue that influences cardiovascular health. More than just a mechanical support around blood vessels [1], PVAT has paracrine activity and produces a wide range of bioactive molecules, including chemokines and proinflammatory adipokines, which have a major impact on the vascular wall and can alter systemic metabolism, inflammation, and vascular tone [2–4]. PVAT controls vascular function in conjunction with the endothelium (Fig. 1).

PVAT may become dysfunctional due to a diversity of mechanisms, making it more susceptible to diseases like atherosclerosis, hypertension, and type 2 diabetes [2, 4–8]. In these conditions, PVAT may be considered a therapeutic target and a biomarker for cardiometabolic disorders [9, 10]. Given this, it is critical to develop new analytical tools that can, noninvasively, characterize

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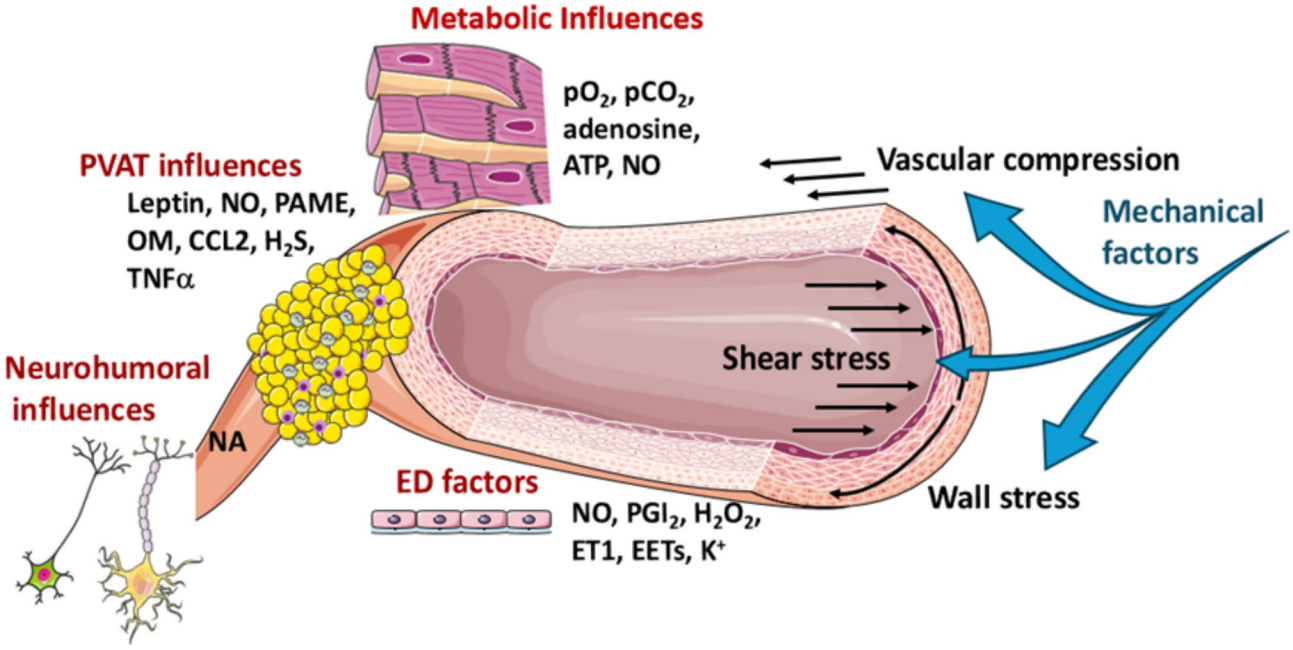

Fig. 1 Schematic representation of various influences that affect blood vessels including metabolic, neurohumoral, perivascular adipose tissue (PVAT) and, endothelial and mechanical factors (vascular compression, shear stress and others). ATP, adenosine triphosphate; CCL2, C-C Motif Chemokine Ligand 2; EETs, epoxyeicosatrienoic acids; ET1, endothelin 1; H_2O_2, hydrogen peroxide; H_2S, hydrogen sulfide, NA, noradrenaline; NO, nitric oxide, OM, omentin; PAME, palmitic acid methyl ester; PGI_2, prostacyclin; TNFα, tumor necrosis factor α.

PVAT and assess its status in order to improve medical diagnostics and comprehend the mechanisms relating lipid metabolism and PVAT to vascular function, inflammation, and insulin sensitivity [1, 2]. Non-invasive methods like magnetic resonance imaging (MRI), computed tomography (CT), and positron emission tomography/computed tomography (PET/CT) offer insights into the morphological and functional aspects of PVAT [10]. These techniques enable the investigation of the spatial connections between PVAT and blood vessels, providing important details about how PVAT affects cardiovascular physiology and pathology [10, 11]. In addition, lipidomics, transcriptomics, and single-cell imaging, along with Raman microscopy, provide insights into the biology of PVAT by revealing its unique cell populations and remarkable heterogeneity [12, 13].

Exploring the crosstalk between PVAT, the immune system, obesity, and vascular disease unveils a complex interplay of cellular and molecular mechanisms that significantly impact cardiovascular health. PVAT, once regarded as an inert tissue surrounding blood vessels, is now recognized as a dynamic endocrine organ actively involved in vascular function regulation and immune modulation [2, 14–16]. In the context of cardiometabolic disease, PVAT undergoes substantial alterations in its composition and function, leading to dysregulation of adipokine secretion, immune cell recruitment, and inflammatory signaling pathways [8, 14–16]. This dysregulated PVAT-immune system crosstalk is a key factor in the development of vascular diseases such as atherosclerosis, vascular inflammation, and hypertension [6, 7, 11, 15]. Targeting key components of this crosstalk may offer novel therapeutic strategies for preventing and treating cardiovascular diseases associated with obesity and PVAT dysfunction.

Definition and localization of PVAT

PVAT refers to the adipose tissue surrounding blood vessels throughout the body. It is distinct from other adipose depots like subcutaneous or visceral fat. In contrast to white (WAT), brown (BAT), beige, and other location-specific adipose tissues PVAT can be identified as a distinct type of adipose tissue [17]. PVAT envelops the outermost layer of the blood vessel wall and serves as a niche for stem and progenitor cells [6, 17, 18]. PVAT is found adjacent to various types of blood vessels including arteries, veins, and arterioles (apart from capillaries, pulmonary, and cerebral blood vessels) [14] forming a sheath-like structure around them and providing mechanical protection. Without an elastic lamina or a physical separating layer, PVAT is in direct contact with the adventitia. This enables the paracrine exchange of numerous factors through bidirectional signaling between PVAT and underlying fibroblasts, vascular smooth muscle cells, or endothelial cells.

PVAT shows regional heterogeneity and variability in its own phenotype [12, 13, 19, 20]. In humans [21] and mice, the PVAT surrounding the abdominal aorta

(AA) and the mesenteric arteries has a predominantly white phenotype, with very few thermogenic adipocytes expressing uncoupling protein 1 (UCP1) [22]. However, the brown-like phenotype of the rodent PVAT surrounding the thoracic aorta (TA) is characterized by multilocular adipocytes and UCP1 expression that is comparable to that of classical brown adipocytes [23–26]]. Patterns of BAT found by PET/CT in the human para-aortic region and surrounding the heart support this [27]. Furthermore, autopsies of adult Siberians showed that approximately 40% of mediastinal periaortic vascular adipose tissue was multilocular and paucilocular in appearance, with up to 73% of cases showing this pattern. Additionally, UCP1 expression was clearly seen in these cases [28].

Unlike humans and large laboratory animals, where the coronary arteries are surrounded by PVAT, mice lack adipose tissue in this area [25, 29, 30]. This heterogenous tissue is increasingly recognized for its dynamic and multifaceted role in maintaining vascular function and overall vascular health.

Historical perspective and research evolution

The study of PVAT has evolved considerably over the past few decades. Initially, PVAT was primarily regarded as a passive structural component surrounding blood and lymphatic vessels, serving as a mechanical support and insulation. However, early observations of its close proximity to blood vessels led researchers to speculate about potential interactions between PVAT and the vascular wall.

In the 1990s and early 2000s, pioneering studies began to shed light on the endocrine and paracrine functions of PVAT [31, 32]. Researchers discovered that PVAT secretes various bioactive molecules, known as adipokines, which can exert both beneficial and detrimental effects on vascular function and inflammation [2]. This discovery marked a paradigm shift in the understanding of PVAT from a mere bystander to an active modulator of vascular physiology and pathology.

Since then, a growing body of evidence has highlighted the intricate crosstalk between PVAT and neighboring blood vessels. Studies have elucidated the role of PVAT-derived factors in the regulation of vascular tone, endothelial function, inflammation, and oxidative stress [6, 8]. Moreover, PVAT has been implicated in the pathogenesis of several cardiovascular diseases, including atherosclerosis, hypertension, and coronary artery disease [2, 6, 33]. Recent advances in imaging techniques, molecular biology, and preclinical models have further accelerated research in the field of PVAT biology. These advancements have enabled investigators to explore the cellular and molecular mechanisms underlying PVAT function in greater detail and to identify novel therapeutic targets for cardiovascular disease [10–14].

Embryonic origin of PVAT

The embryonic origin and genetic signature of PVAT adipocytes are very complicated due to their heterogeneity [34]. Chang and co-workers [24] have referred that TA PVAT, AA PVAT and periaortic arch exhibited a common smooth muscle22α-expressing precursor as vascular smooth muscle cells. In addition, a lack of peroxisome proliferator-activated receptor gamma (PPARγ) in smooth muscle cells resulted in PVAT deprivation in mice [24]. In contrast, mesenteric PVAT displayed a transcriptional profile comparable to visceral adipose tissue and the same Wilms tumor 1 (Wt1)-positive progenitor [35]. Similarly, epicardial adipocytes developed from Wt1-expressing mesenchymal cells that were converted from T-box 18-expressing epicardial progenitors and differentiated into mature adipocytes once PPARγ expression was activated [35, 36].

PVAT adipocytes have intricate developmental beginnings. The TA PVAT depot is made up of three strip-shaped adipose tissues: anterior, left lateral, and right lateral. Ye and colleagues found that 89% of anterior TA PVAT [13% myogenic factor 5(Myf5) +] and 62% of left lateral TA PVAT (24% Myf5 +) were SM22α positive [37]. The left lateral TA PVAT expanded quicker than the anterior TA PVAT [37]. The authors later observed that periaortic arch adipose tissue, a form of brown adipose tissue encircling the ascending aorta, arose from at least three types of precursors, including Sm22α+neural crest cells, Myf5+progenitors, and an unknown origin [38]. However, neural crest cells did not participate in the creation of TA PVAT [37]. More recently, Angueira and colleagues established unequivocally that in an 18-day-old embryo, the thoracic aorta was primarily surrounded by fibroblasts expressing platelet-derived growth factor receptor alpha (Pdgfra +) [39]. This study enhances the understanding of PVAT's embryonic origins, particularly the differential contributions of fibroblastic progenitors and the role of transcriptional regulators like Early B-Cell Factor-2 in defining the thermogenic potential of PVAT in various regions [39].

Further research is required to elucidate the diverse origins of PVATs, which result in phenotypic and secretory heterogeneity between PVAT depots.

Physiology and functions of PVAT

PVAT is considered by many as the four layer of blood vessel wall [17], playing a crucial role in the regulation of vascular function and homeostasis through a variety of physiological mechanisms (Fig. 2). Understanding its composition and functions is essential for comprehending its impact on cardiovascular health.

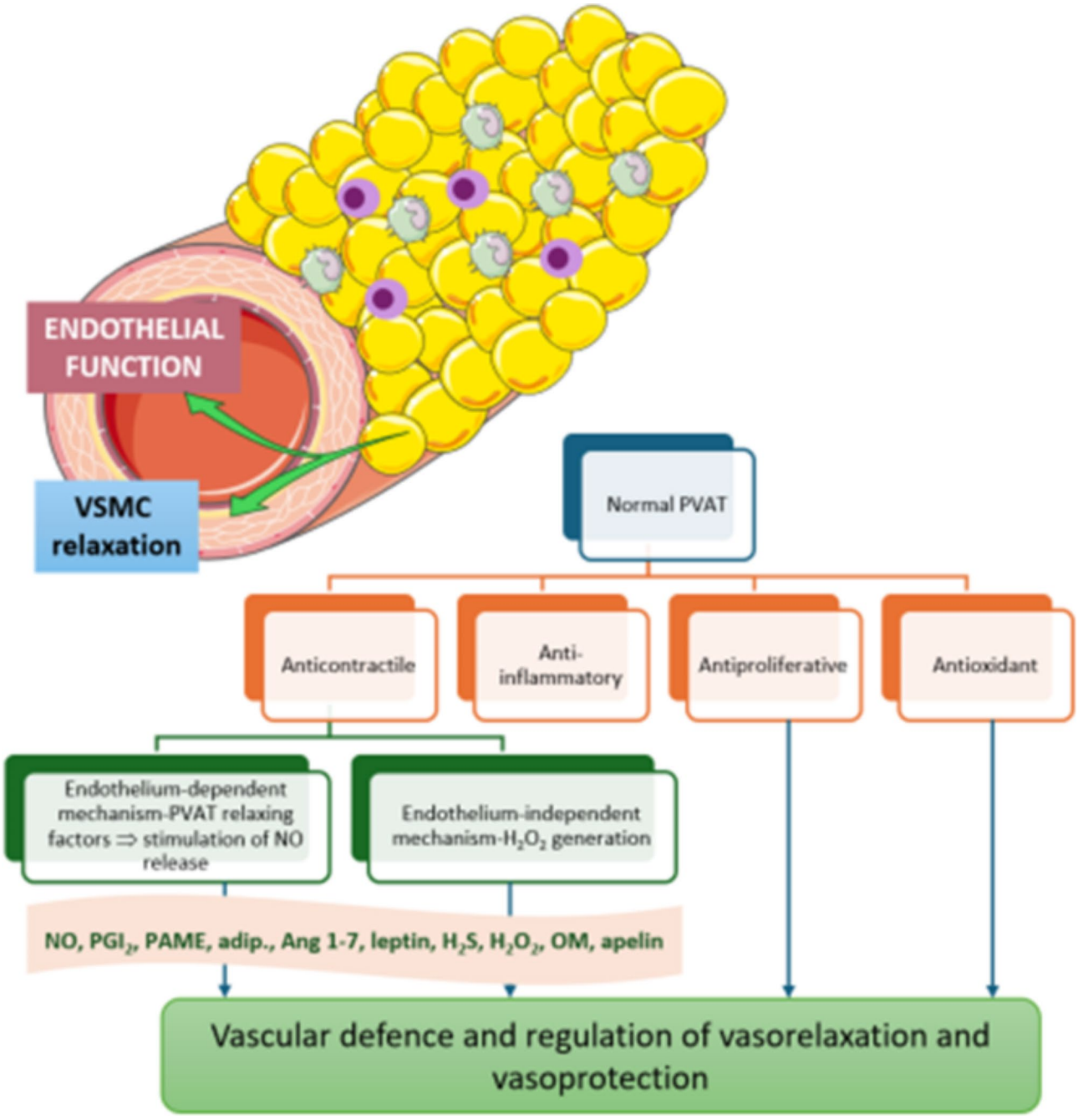

Fig. 2 Physiological functions of perivascular adipose tissue (PVAT). PVAT regulates vascular tone, blood flow, redox balance, angiogenesis, and inflammation by releasing vasoactive and vasocrine factors, as well as adipokines and cytokines, which act on the VSMC and endothelium. Ang 1–7, angiotensin 1–7; adip., adiponectin; H_2O_2, hydrogen peroxide; H_2S, hydrogen sulfide, NO, nitric oxide, OM, omentin; PAME, palmitic acid methyl ester; PGI_2, prostacyclin; VSMC, vascular smooth muscle cells; TNFα tumor necrosis factor α.

PVAT composition and metabolic activity

PVAT is primarily composed of adipocytes that make up the majority of PVAT by volume, but just one-third of WAT's total cell count—also comprising white adipocytes—are found in PVAT [34]. These PVAT-resident stromal cells have the ability to differentiate into brown or white adipocytes [40]. PVAT possesses traits of both BAT and WAT. Noteworthy, PVAT adipocytes exhibit distinct metabolic characteristics compared to those in other adipose depots. These adipocytes are metabolically active, displaying higher rates of lipolysis and fatty acid uptake. They also express unique sets of genes involved in lipid metabolism, adipokine secretion, and inflammation [3, 6, 8]. The metabolic activity of PVAT adipocytes

is tightly regulated by various factors, including hormonal signals, neuronal inputs, and local environmental cues [2, 14]. In addition, the chemical composition and biological activity of PVAT are strongly altered by age and dietary patterns. The degree of lipid unsaturation in different types of adipose tissues varies with animal age. Notably, the abdominal aorta and mesenteric artery have significantly larger quantities of unsaturated lipids inside their respective PVATs than the thoracic aorta, and aging causes an increase in unsaturated lipids within PVAT [41]. Adipocyte dysfunction, characterized by impaired lipid handling and dysregulated adipokine secretion, can disrupt PVAT homeostasis and contribute to cardiovascular dysfunction [14, 15, 42].

PVAT contains a variety of cell types in addition to adipocytes, preadipocytes, and adipocyte stem cells. These cells include mesenchymal stem cells, T-cells, B cells, fibroblasts, nerves, pericytes, endothelial precursor cells, and macrophages [43, 44]. The stromal vascular fraction (SVF) is the term used to describe this cell population [1]. The cell population that is left over after adipocytes, connective tissue, and blood are extracted from any adipose tissue is known as the SVF [45]. Because of its potential for regeneration in conditions like diabetes, the stem cell fraction has historically been isolated using enzymes like collagenase [45]. A recent study by Thompson et al. employed single-nuclei RNA sequencing characterized the cellular composition of TA PVAT and subscapular BAT in male Dahl salt-sensitive rats [46]. This study revealed significant insights into the distinct cellular environments within PVAT. This bulk gene expression analyses of BAT and TA PVAT in mice have demonstrated a high degree of similarity between the two brown adipose tissue depots [26, 46].

Endocrine and paracrine functions of PVAT

PVAT secretes a wide array of bioactive adipokines that exert both endocrine and paracrine effects on neighboring tissues, including blood vessels. These adipokines include adiponectin, leptin, resistin, interleukins, and tumor necrosis factor α (TNFα), among others [2].

Adipokines released by PVAT can influence vascular function by modulating endothelial cell behavior, smooth muscle cell contraction, and immune cell activation [2, 14, 31, 32, 47]. For example, adiponectin promotes endothelial nitric oxide (NO) production and vasodilation [48, 49]. In addition, mouse TA PVAT secretes several anti-inflammatory adipokines, including neuregulin 4(NRG4), and interleukin (IL)-10 [3, 50, 51], which can reduce inflammation and oxidative stress. In contrast, proinflammatory adipokines like TNFα and interleukins can induce endothelial dysfunction, oxidative stress, and vascular inflammation [14, 52].

Additionally, PVAT-derived adipokines can act in a paracrine manner to regulate vascular tone and blood flow in response to local stimuli. By releasing vasoactive factors such as hydrogen peroxide, hydrogen sulfide (H_2S), palmitic acid methyl ester, angiotensin (Ang) 1–7, and C1q/tumor necrosis factor-related protein 9, and other adipocyte-derived relaxing factors (Fig. 2), PVAT can modulate vascular smooth muscle cell relaxation and contraction, thereby influencing vascular tone and blood pressure regulation [2, 47, 53].

PVAT secretes molecules that are involved in metabolism, including chemokines, adipokines, and hormone-like substances like resistin, adiponectin, and leptin, as well as free fatty acids and other vasoregulators [2, 14, 25, 42]. As a result, the interaction between PVAT and blood vessels suggests that it is essential to maintaining vascular homeostasis [53]. Disease-promoting factors are secreted by PVAT dysfunction, which is caused by a disruption of the proper mutual relationship [8, 14, 42]. Consequently, aberrant alterations occur that lead to different types of diseases in the blood vessel's underlying layers. PVAT dysfunction may serve as a precursor to vascular disease. In order to clarify the role of PVAT in pathological conditions and diseases, such as inflammation [3, 11, 19, 33], obesity [48, 54, 55], insulin resistance and type 2 diabetes [7, 8, 49], hypertension [5, 6, 56], and atherosclerosis [2, 5, 6, 10], a number of animal models have been used. Given the notable variability in PVAT's depot- and function-dependent variability as a target for metabolic and cardiovascular diseases, it is imperative to explore novel approaches for characterizing distinct PVAT phenotypes and tracking changes in PVAT across a range of processes, including browning and pathology-related changes.

Role in vascular homeostasis and regulation

PVAT plays a critical role in maintaining vascular homeostasis by providing structural support to blood vessels [1] and dynamically regulating vascular tone and blood flow. Through its paracrine actions, PVAT can modulate vascular function in response to physiological stimuli such as changes in blood flow, shear stress, and metabolic demand [1, 2, 6, 14]. Furthermore, PVAT has been implicated in the regulation of vascular remodeling, angiogenesis, and inflammation, processes that are integral to the pathogenesis of cardiovascular diseases such as atherosclerosis and hypertension [2, 5, 6, 10]. Dysregulation of PVAT function, characterized by adipocyte hypertrophy, inflammation, and fibrosis, can impair vascular homeostasis (Fig. 3), and contribute to the development of cardiovascular dysfunction [11, 48, 57, 58].

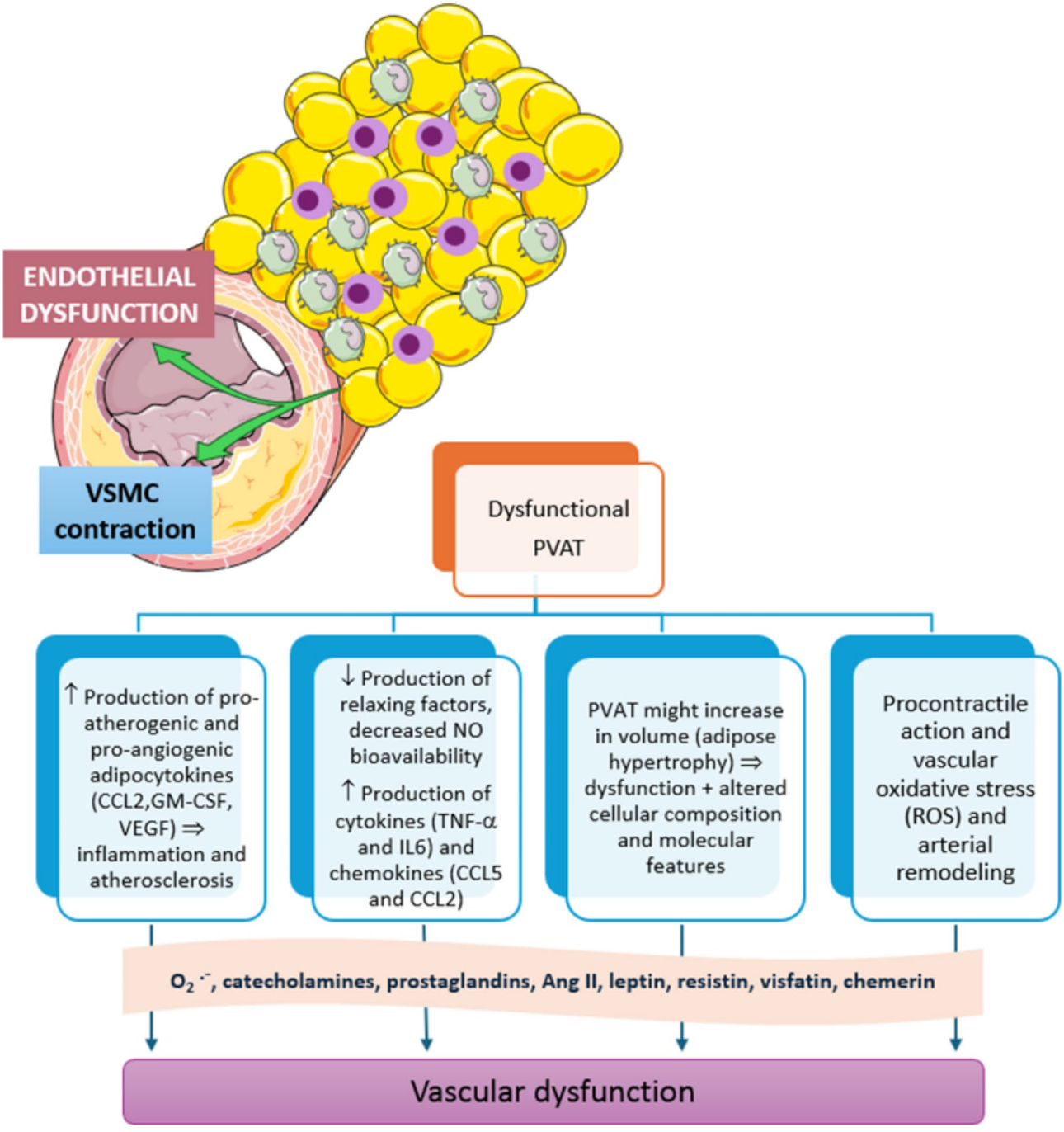

Fig. 3 Dysfunctional perivascular adipose tissue (PVAT) leads to several changes that ultimately trigger vascular dysfunction. Ang II, angiotensin II; CCL2, C-C Motif Chemokine Ligand 2; CCL5, C-C Motif Chemokine Ligand 5; GM-CSF, granulocyte-macrophage colony-stimulating factor; IL6, interleukin-6; TNFα, tumor necrosis factorα; VEGF, vascular endothelial growth factor.

Pathophysiological links between PVAT and cardiometabolic diseases

The bi-directional crosstalk between PVAT and the aorta wall is the cause of PVAT dysfunction in cardiometabolic diseases, such as type 2 diabetes, obesity, atherosclerosis, inflammation, hypercholesterolemia [2, 4–8, 59–64]. When adjusted for body mass index (but not visceral adipose tissue), the thoracic peri-aortic fat mass in humans is correlated with hypertension, diabetes, and aortic/coronary calcification [65]. At first, PVAT was believed to provide blood arteries with mechanical and structural support while simultaneously having the capacity to "inside-out" detect signals emitted by the

endothelium and smooth muscle cells in the vessel wall [1, 66].

It is now recognized that PVAT releases a range of bioactive substances, such as adipokines, and that paracrine "outside-in" activity affects the vascular environment nearby. PVAT signals can impact vascular health in a positive or negative way, contingent on the molecules and their concentrations [2, 11, 66, 67]. PVAT interacts intricately with lipids in the context of diabetes, obesity, and atherosclerosis. Dyslipidemia, adipocyte hyperplasia, and hypertrophy result from an imbalanced lipid storage and release system [68]. Insulin resistance affects PVAT and leads to dysregulation in lipid metabolism, which affects the lipid composition of PVAT. Inflammatory adipokines are released by dysfunctional PVAT [15, 19, 56], which also promote endothelial dysfunction, attract immune cells to the arterial wall, and help in the buildup of fat and the development of atherosclerotic plaques, affecting shear stress and blood flow [1, 2, 6, 15].

The intricate interplay between PVAT and diabetes is a topic of growing interest in cardiovascular research. Dysregulation of PVAT function contributes to the pathogenesis of diabetes and vice versa, creating a bidirectional relationship with profound implications for vascular health [7, 8, 10, 49].

Adipokine dysregulation and insulin resistance

PVAT dysfunction in diabetes is characterized by alterations in adipokine secretion and insulin sensitivity [7, 8, 49]. Adipokines, such as adiponectin and leptin, play crucial roles in glucose metabolism, insulin sensitivity, and inflammation [68]. In diabetes, there is often dysregulation in the secretion of these adipokines from PVAT [7, 8, 49].

Adiponectin, an adipokine with anti-inflammatory and insulin-sensitizing properties, is typically downregulated in PVAT of individuals with diabetes [49]. Low levels of adiponectin are associated with obesity, diabetes and hypertension and other cardiovascular disorders. Reduced adiponectin levels contribute to insulin resistance and impaired glucose uptake in peripheral tissues [68]. In contrast, high levels of adiponectin can be detrimental and have been linked with cardiovascular disease [69] "the adiponectin paradox". Conversely, leptin, which regulates energy balance and appetite, may be elevated in diabetes, promoting inflammation and insulin resistance [68]. Leptin resistance is typically associated with obesity and high adipose tissue levels.

The dysregulated secretion of adipokines from PVAT contributes to systemic insulin resistance, a hallmark of type 2 diabetes. Insulin resistance impairs glucose uptake in insulin-sensitive tissues, leading to hyperglycemia and dyslipidemia [68]. Moreover, insulin resistance in PVAT itself disrupts adipocyte function and exacerbates adipose tissue inflammation, creating a vicious cycle that further promotes metabolic dysfunction [2, 14, 66].

Inflammatory pathways and insulin sensitivity

Inflammation is a key pathophysiological feature linking PVAT dysfunction and diabetes [8, 44]. PVAT in individuals with diabetes exhibits increased expression of proinflammatory cytokines, such as TNFα, IL6, and chemokine (C-C motif) ligand 2 (CCL2). These cytokines stimulate insulin resistance by impairing insulin signaling pathways and promoting adipose tissue inflammation [10].

Inflammatory signaling pathways activated in PVAT participate in the development of systemic insulin resistance and endothelial dysfunction, which are central to the pathogenesis of diabetes-related vascular complications. Chronic low-grade inflammation in PVAT exacerbates adipocyte dysfunction, leading to adipose tissue remodeling, fibrosis, and impaired adipokine secretion [11, 48, 57, 58].

PVAT dysfunction in diabetic vascular complications

PVAT dysfunction contributes to the pathogenesis of diabetic vascular complications, including atherosclerosis, endothelial dysfunction, and vascular remodeling. PVAT dysfunction is also seen as diabetes mellitus progresses, much like obesity. But given that obesity is regarded as a major modifiable risk factor for the onset and progression of diabetes mellitus [70], it makes sense to hypothesize that dysfunctional PVAT in the context of diabetes may, through comparable mechanisms, partially cause detrimental effects on the vasculature. It is in fact challenging to focus only on studying the function of diabetic PVAT because obese individuals and animal models are frequently linked to diabetes. Some research on humans and animals has revealed that PVAT dysfunction in diabetes damages vascular homeostasis by elevating inflammation and oxidative stress [8, 49]. In the diabetic db/db mice, whitening of PVAT has also been seen [59], suggesting elevated cardiovascular risks. Dysregulated secretion of adipokines and proinflammatory cytokines from PVAT promotes vascular inflammation, oxidative stress, and endothelial dysfunction, predisposing individuals with diabetes to accelerated atherosclerosis and cardiovascular events [8, 49]. In a previous study we have investigated the involvement of diabetic PVAT in vascular dysfunction using a nonobese rodent model of type 2 diabetes mellitus (male Goto-Kakizaki diabetic rats). We demonstrated that periaortic PVAT markedly reduced vascular function in nonobese diabetic rats, elevated nitrotyrosine levels in the aortic PVAT, inhibited antioxidant enzymes [e.g, manganese superoxide dismutase (MnSOD) and catalase] in the thoracic PVAT, and upregulated the expression of inflammatory markers (e.g., CCL2 and CD36) in

the diabetic PVAT [8]. These findings provide evidence that diabetic PVAT has detrimental effects on the vasculature. An additional human study found a positive correlation between $O_2^{\bullet-}$ produced by nicotinamide adenine dinucleotide phosphate (NADPH) oxidase and the level of adiponectin in PVAT. Additionally, this study offered experimental support that decreased adiponectin levels stimulated NADPH oxidase in type 2 diabetic patients, whereby the diabetic PVAT could detect the increased NADPH oxidase activity to cause an increase in adiponectin [49]. These findings demonstrate the role of an adipocytokine derived from PVAT in the regulation of vascular function in diabetes mellitus.

Vascular insulin resistance is an important hallmark in atherosclerosis [71]. Importantly, dysfunctional PVAT contributes to the development of vascular insulin resistance, impairing the vasodilatory capacity of blood vessels and promoting vasoconstriction and hypertension [60]. Using db/db mice it was found that diabetic PVAT was linked to proinflammatory cytokines (e.g., IL6, TNFα, and Interferon-γ) being upregulated, macrophage polarization to the proinflammatory M1 phenotype, and whitening [i.e, decreased UCP1 expression] [59]. However, the role of obesity in db/db mice could not be completely ruled out. Future research will compare the detrimental effects of PVAT in diabetics and obese people. Indeed, PVAT-derived factors can directly influence vascular smooth muscle cell proliferation, migration, and extracellular matrix remodeling, contributing to vascular remodeling and arterial stiffness [2, 55, 61, 62].

The impact of obesity on PVAT function

Obesity exerts profound effects on several adipose tissue depots including PVAT, altering its structure, function, and secretory profile [14, 54–56, 63]. Obese patients with metabolic syndrome completely lose the anticontractile effect of PVAT in human small arteries (obtained from a subcutaneous gluteal fat biopsy) [64]. Lee and co-workers utilized CT imaging to compare the variations in AA PVAT fat attenuation index (FAI) between patients with moderate metabolic syndrome and healthy individuals. They discovered that higher abdominal PVAT volume was found to be independently associated with the prevalence of metabolic syndrome. Furthermore, lower AA PVAT FAI was associated with mild metabolic abnormalities indicating that AA PVAT imaging may serve as a biomarker for cardiometabolic risk [72]. Understanding the impact of obesity on PVAT is essential for elucidating its role in obesity-related cardiovascular complications and possible development of preventive approaches [54].

Adipose tissue expansion and remodeling

Obesity is characterized by excessive adipose tissue expansion, leading to adipocyte hypertrophy, hyperplasia, inflammatory cells infiltrating the tissue, modifications to the extracellular matrix, and altered patterns of adipokine secretion [73]. PVAT undergoes similar expansion in response to obesity [and presence of an excessive energy intake such as from a high-fat diet (HFD)], resulting in increased adipocyte size and mass [74, 75] and shift toward a whitening phenotype [76] Adipose tissue expansion induces remodeling of the extracellular matrix and alterations in adipocyte morphology, impairing PVAT function [1, 68]. As PVAT expands, adipocytes become dysfunctional, exhibiting altered lipid metabolism, increased lipolysis, and impaired adipokine secretion. Dysregulated adipocyte function contributes to adipose tissue inflammation, oxidative stress, and insulin resistance, creating a proinflammatory microenvironment within PVAT [68].

Adipokine dysregulation and inflammation

Obesity-induced inflammation is a hallmark of PVAT dysfunction. PVAT becomes a significant source of proinflammatory adipokines such as leptin, TNFα, and IL6, while anti-inflammatory adipokines such as adiponectin are reduced. These alterations in adipokine secretion create a proinflammatory milieu within PVAT, promoting the recruitment and activation of immune cells. Activated immune cells release cytokines and chemokines, further amplifying the local inflammatory response and contributing to endothelial dysfunction, vascular damage and insulin resistance [77, 78].

Macrophages play a central role in PVAT inflammation, adopting a proinflammatory phenotype (M1) in response to obesity-associated stimuli. M1 macrophages secrete cytokines such as TNFα, IL6, and interleukin-1β (IL1β), which promote adipocyte dysfunction and vascular inflammation [8, 77]. These activated macrophages also produce reactive oxygen species (ROS), cytokines, and matrix metalloproteinases, which promote vascular smooth muscle cell proliferation, migration, and extracellular matrix remodeling [77]. Additionally, other immune cells, including T cells and mast cells present in PVAT contribute to local inflammation and vascular dysfunction through the release of inflammatory mediators and direct interactions with vascular cells, contribute to PVAT inflammation and metabolic dysfunction [77].

Therefore, PVAT malfunction brought on by obesity increases the invasion of immune cells such as monocytes, macrophages, and dendritic cells, which in turn induces inflammation in the surrounding microenvironment. The quantity and level of activation of resident immune cells in PVAT differ significantly during obesity. For example, thoracic and mesenteric PVATs of HFD fed Dahl salt-sensitive hypertensive rats showed hyperactivation of regulatory T cells and M2 macrophages [79]. In addition, CCL2, TNFα, IL6, leptin, visfatin, and resistin,

are highly expressed in the microenvironment due to these immune cells with a proinflammatory milieu in PVAT. On the other hand, malfunctioning PVAT results in decreased levels of anti-inflammatory adipocytokines, specifically adiponectin [47]. As a result, inflammation in obese PVAT increases ROS production, especially $O_2^{\bullet-}$ and H_2O_2 [8, 48, 55]. Pharmacologically, vascular function could be significantly restored by co-incubating obese PVAT-containing aorta segments with free radical scavengers and TNFα inhibitors [80]. Concomitantly, decreased ROS generation and vasocontraction were seen in PVAT from obese male mice lacking the TNFα receptor [80]. Conversely, reduced MnSOD expression, enhanced whitening in PVAT, diminished anticontractile action, and mitochondrial deformation were all linked to IL18 deficiency in PVAT [81]. These investigations demonstrate the relationship between inflammation and oxidative stress in PVAT and surrounding vasculature, especially when vascular dysfunction develops. In order to reduce the risk of cardiovascular disease, therapeutic strategies that encourage browning in PVAT may also reduce inflammation and oxidative stress.

Browning of PVAT has gained increased attention in this field [3, 82]. Multiple processes, including cold stimuli or hormones such as fibroblast growth factor 21, atrial natriuretic peptide, and bone morphogenetic proteins, can modify white-like adipose tissue into beige adipose tissue via a "browning" mechanism [5, 83]. Previous research has demonstrated that vascular damage causes PVAT to beige (have a brown adipose tissue-like phenotype), which fine-tunes the inflammatory response and hence vascular remodeling as a protective strategy. In a mouse model of endovascular damage, macrophages aggregate in PVAT, resulting in a beiging phenotype. Inhibition of PVAT beiging by genetically silencing PR Domain containing 16, a critical regulator of beiging, worsens inflammation and vascular remodeling after injury. Conversely, activating PVAT beiging reduces inflammation and abnormal vascular remodeling. Significant beiging is seen in the diseased aortic PVAT of individuals with acute aortic dissection. Thus, vascular damage stimulates the beiging of nearby PVAT with macrophage accumulation, and NRG4 produced from the beige PVAT allows alternative activation of macrophages, leading to the resolution of vascular inflammation [84]. In addition, it was previously observed that overexpressing mitoNEET in brown adipocytes, particularly PVAT adipocytes, dramatically reduced arterial stiffness and atherosclerosis [85, 86].

Importantly, vascular anomalies associated with obesity may potentially be caused by epigenetic modifications in PVAT adipocytes. It was demonstrated in a prior study that the expression of peroxisome proliferator activated receptor gamma coactivator 1α (PGC-1α) in PVAT and UCP1 in the epicardial adipose tissues of rats given a HFD was impaired by the epigenetic suppression of PGC-1α in PVAT [87]. Although the precise mechanism is still mostly unknown, a recent study reveals that activating transcription factor 3 may be involved in epigenetic control of PVAT and elicit an anti-inflammatory impact against obesity-related vascular damage [54]. To fully understand the function and mechanism of epigenetic regulation in obese PVAT in relation to the accumulation of ROS and the control of inflammation, further thorough research is needed.

Altered adipokine secretion and vascular effects

Obesity-induced alterations in adipokine secretion from PVAT have profound effects on vascular function and health. Proinflammatory adipokines released from obese PVAT promote endothelial dysfunction, oxidative stress, and vascular inflammation, predisposing individuals to atherosclerosis and cardiovascular disease [14, 48, 55].

Leptin, a proinflammatory adipokine elevated in obesity, promotes endothelial dysfunction by inducing oxidative stress and inflammation. Resistin, another proinflammatory adipokine, impairs endothelial function and promotes vascular smooth muscle cell proliferation and migration, contributing to vascular remodeling and arterial stiffness [14, 48, 55].

Conversely, adiponectin, an anti-inflammatory adipokine with vasoprotective effects, is typically reduced in obese individuals. Adiponectin controls endothelial function by phosphorylating of nitric oxide synthase (NOS) and through a decrement in ROS production (reducing NADPH oxidase), which raises NO bioavailability in the vessel wall [48, 88]. Decreased adiponectin levels impair endothelial function and promote vascular inflammation, increasing the risk of cardiovascular disease.

The dysregulated PVAT-immune system crosstalk exacerbates vascular dysfunction by impairing endothelial cell function and promoting endothelial activation [8]. Adipokines and inflammatory cytokines released from PVAT induce endothelial cell activation, characterized by increased expression of adhesion molecules (e.g., vascular cell adhesion molecule 1, intercellular adhesion molecule 1) and proinflammatory mediators (e.g., CCL2, IL8) [48]. This endothelial activation facilitates immune cell adhesion and infiltration into the vessel wall, initiating the early stages of atherosclerosis and promoting plaque formation [2].

Oxidative stress and vascular redox system in PVAT dysfunction

Oxidative stress and dysfunction in the vascular redox system are critical mechanisms underlying PVAT dysfunction. The excessive generation of ROS, coupled with impaired antioxidant defenses, promotes inflammation,

vascular remodeling, and a reduction in nitric oxide bioavailability, leading to vascular diseases [2, 44, 48, 89].

Several molecular pathways are involved in oxidative stress and PVAT dysfunction including increased expression of nuclear factor kappa B (NF-κB) [90], and impaired nuclear factor erythroid 2–related factor 2 activity that reduces the antioxidant response and exacerbates oxidative damage [91]. Protein kinase C and mitogen-activated protein kinases are also activated by oxidative stress [92, 93]. These pathways modulate various aspects of vascular tone, inflammation, and vascular smooth muscle cell function, contributing to the progression of vascular diseases [94]. In addition, previous research has shown that obesity causes changes in circulating plasma concentrations in human vascular disease as well as an imbalance in Wingless-related integration site 5 A (WNT5A) and secreted frizzled-related protein 5 (SFRP5) expression in PVAT and other adipose tissue depots like thoracic adipose tissue [95, 96]. Recent work demonstrated that WNT5A receptors Fzd2 and Fzd5, which are involved in non-canonical Wnt signaling in human arteries, are upregulated in obesity [97]. This research highlighted the receptors of WNT5A, its interaction with SFRP5, and the downstream signaling network as the molecular connections between obesity and vascular complications in humans.

Hemodynamic alterations and hypertension

PVAT's anti-contractile characteristic is notably lost during obesity [48, 54, 55], which may have a role in the etiology of hypertensive cardiovascular diseases. In obesity, dysfunctional PVAT contributes to hemodynamic alterations and hypertension through multiple mechanisms [6, 14]. Enhanced sympathetic nervous system activity and impaired vasodilatory capacity of PVAT-derived factors, such as adiponectin and H_2S, lead to vasoconstriction and increased vascular tone [14, 48, 55]. Moreover, PVAT-mediated inflammation and oxidative stress contribute to endothelial dysfunction, impaired NO bioavailability, and increased vascular resistance, further exacerbating hypertension and promoting vascular remodeling [6].

Blood pressure regulation and vascular homeostasis are closely linked to the renin-angiotensin-aldosterone system (RAAS) [98]. Adipose tissues, such as PVAT, can produce several components of the RAAS, which are implicated in the development of arterial stiffness and hypertension [55]. Adipocyte hypertrophy markedly increased the production of aldosterone, angiotensinogen, and angiotensin II (Ang II) in PVAT of obese patients [99]. By inhibiting endothelial NOS (eNOS) activity in vascular endothelial cells, Ang II increases oxidative stress and decreases NO bioavailability through the Ang II type 1 receptor [100]. In addition, Ang II stimulates the production of vasoconstrictors that degrade vascular function and cause oxidative stress, such as endothelin-1 and prostanoids produced from cycloxygenase-1 [101]. It was demonstrated that a deficiency in bone morphogenetic protein 4 in PVAT raises Ang II and angiotensinogen levels as well as vascular oxidative stress [102].

Noteworthy, PVAT's paracrine activities help regulate circadian blood pressure and may explain the clinical findings linked with the dipper and non-dipper phenotypes in humans [103].

Periaortic PVAT, particularly that surrounding the thoracic aorta, functions in conjunction with the rest of the vessel to determine the stiffness of the aorta [65, 104]. When PVAT was taken into account, the mechanically measured thoracic aortic stiffness decreased [105]. Both IL-6 [106] and advanced glycation end products [106, 107] contributed, at least in part, to arterial stiffness in the mouse through their actions within PVAT. Importantly, in the knockout mouse specific to PPARγ smooth muscle cells, mice do not develop PVAT around the thoracic aorta, and compared to the wild type, the knockout mouse had a higher pulse wave velocity, which is a marker for aortic stiffness [24]. In addition, the PPARγ activator pioglitazone ameliorates PVAT phenotype and may have the effect of reducing aortic stiffness in ob/ob mice [108]. Recently, research confirmed that TA PVAT cells have mechanotransducers [46] and ought to be taken into account mechanistically when evaluating stiffness [24].

Novel methods to assess PVAT dysfunction

Raman-based methods, which are well-suited for studying lipids, were utilized in animal models of cardiovascular and cardiometabolic diseases [109]. Raman spectroscopy methods can be combined with other techniques, such as Raman fiber probes to evaluate dietary fat accumulation in subcutaneous and visceral adipose tissue [110] or with Two-photon Excited Fluorescence Microscopy and Second Harmonic Generation to visualize lipid droplets, macrophages, and collagen fibers [111]. The suggested spectroscopic marker, lipid unsaturation degree, was found to be clearly distinct in periaortic PVAT and was influenced by the age of the animal models [41]. Raman spectroscopy techniques were also applied to PVAT. It was possible to identify the pathological alterations in atherosclerosis [112], and obesity [57, 113] due to PVAT lipid alterations. It was previously shown that there is a direct correlation between the increased level of unsaturation of lipids in PVAT and the increase in the lipid-to-protein ratio in the aorta wall in the murine model of atherosclerosis (ApoE $^{-/-}$/LDLr $^{-/-}$ male mice) [112]. Using Coherent anti-Stokes Raman spectroscopy in conjunction with multimodal nonlinear optical imaging, it was possible to identify molecular

site-specific alterations in TA PVAT at various stages of atherosclerosis in male ApoE$^{-/-}$ mice [58].

Mechanisms of PVAT involvement in cardiovascular diseases

PVAT is widely acknowledged as a major player in the pathogenesis of various cardiovascular diseases. Understanding the mechanisms through which PVAT contributes to these conditions is crucial for developing targeted therapeutic strategies. Here, we explore the involvement of PVAT in atherosclerosis, hypertension, and arrhythmogenesis, highlighting its multifaceted role in cardiovascular pathology.

Atherosclerosis and Plaque development

PVAT plays a significant role in the development and progression of atherosclerosis [2, 6], a chronic inflammatory condition characterized by the accumulation of lipids and inflammatory cells within the arterial wall [114]. PVAT-derived factors contribute to atherosclerosis through several mechanisms [2, 6].

Inflammation and immune activation

PVAT secretes proinflammatory cytokines and chemokines that promote the recruitment and activation of immune cells within the arterial wall, exacerbating vascular inflammation and atherosclerotic plaque formation [2, 6]. Importantly, PVAT and resident mesenchymal stem cells may have a role and be considered as a new therapeutic technique for improving cardiac protection [115].

A recent study used co-culture studies to investigate the crosstalk between resident mesenchymal stem cells (ASCs) and vascular smooth muscle cells. ASCs were obtained in the adventitia of the left anterior descending PVAT, demonstrating differentiation capacity and angiogenic potential. ASCs removed from PVAT of non-ischemic and ischemic hearts exhibited varying tissue factor (TF) expression levels, VSMC recruitment capacity via the extracellular signal-regulated kinases 1/2-ETS1 signaling axis, and angiogenesis potential [115]. Induced TF overexpression in ASCs isolated from ischemic PVAT restored their angiogenic capacity in subcutaneously implanted plugs in mice, whereas silencing TF in ASCs reduced the proangiogenic potential of non-ischemic ASCs. These findings describe a new mechanism by which PVAT-derived ASCs regulate VSMC activity during angiogenesis, mediated through TF expression. Targeting TF regulation in ASCs could provide a new therapeutic approach for enhancing cardiac protection [115].

Dyslipidemia and lipid accumulation

Dysregulated adipokine secretion from PVAT can disrupt lipid metabolism and promote the accumulation of lipids within the arterial wall, contributing to the formation of foam cells and fatty streaks, early hallmarks of atherosclerosis [116].

Vascular remodeling and endothelial dysfunction

PVAT-derived factors influence vascular remodeling and endothelial function, impairing the integrity of the arterial wall and predisposing it to atherosclerotic lesion formation. Vascular pathological conditions cause the PVAT to secrete fewer anti-inflammatory factors and more proinflammatory cytokines, which intensifies local inflammation and promotes the growth of neointima [8]. Proinflammatory factors like IL6 and TNFα, resistin, visfatin, chemerin, leptin, and CCL2 are secreted [8, 14]. PVAT produces ROS in the intima in response to damage, and inflammatory cells also infiltrate the intima [13]. Damage to the vascular wall causes an imbalance by elevating proinflammatory adipocytokines and reducing PVAT-derived vasoprotective factors. Dysfunctional PVAT exacerbates endothelial dysfunction and promotes oxidative stress, inflammation, and endothelial cell apoptosis, further driving atherosclerosis progression.

A recent study revealed that the PVAT of the mouse thoracic aorta contains two primary clusters of mesenchymal stem/stromal cells [44]. One cluster was enriched for genes linked to the differentiation of vascular smooth muscle cells while the other cluster was linked to angiogenic and adipogenic potential [44]. PVAT may influence vascular remodeling, as evidenced by the significant promotion of neointima formation following transplantation of the mesenchymal stem/stromal cells obtained from PVAT into a vein graft model [44].

PVAT phenotype and lipid content

Kim and co-workers examined the relationship between the quantity and size of lipid droplets in TA PVAT and the measurement of UCP1 expression. They discovered UCP1 expression loss, activated TGF-β signaling, and fibrosis in the PVAT region next to an atherosclerotic plaque [58]. Using spectral modeling and fiber-optic Raman spectroscopy, the degree of lipid unsaturation and the carotenoid content may function as markers of PVAT functional status [117]. Previous research has described that male mice with the S961 peptide showed increased lipid unsaturation, correlated with decreased UCP1 and adiponectin expression, suggesting a loss of vasoprotective and BAT functions [118]. Raman-based PVAT assessment shows potential as a diagnostic method for quickly characterizing the PVAT phenotype, potentially used intraoperatively in medical settings [109].

Hypertension and vascular tone regulation

PVAT plays a crucial role in regulating vascular tone and blood pressure through its vasoregulatory effects on

adjacent blood vessels [5]. Dysfunctional PVAT contributes to the development of hypertension through various mechanisms [6].

Vasoactive factors

PVAT-derived adipokines and vasoactive molecules influence vascular smooth muscle cell contraction and relaxation , modulating vascular tone and blood pressure regulation. Dysregulated secretion of vasoactive factors from PVAT can disrupt vascular homeostasis and promote vasoconstriction, leading to hypertension [5, 6, 56].

Endothelial dysfunction

PVAT-derived factors can impair endothelial function and NO production, compromising endothelium-dependent vasodilation and promoting vasoconstriction [55, 74, 88]. Endothelial dysfunction contributes to increased vascular resistance and hypertension, exacerbating cardiovascular risk [52].

Inflammation and oxidative stress

Chronic low-grade inflammation in PVAT promotes oxidative stress and vascular inflammation, which contribute to endothelial dysfunction, arterial stiffness, and hypertension [2, 6, 104–106]. In addition, chronic low-grade inflammation in PVAT disrupts adipokine secretion, impairing the balance between proinflammatory and anti-inflammatory adipokines. Adipocytes in obese PVAT exhibit altered adipokine secretion, with increased release of proinflammatory adipokines such as leptin, resistin, and TNFα, and decreased secretion of anti-inflammatory adipokines such as adiponectin [2, 6]. Inflammatory cytokines and ROS released from dysfunctional PVAT disrupt vascular homeostasis and contribute to hypertension pathogenesis [6, 53, 56, 102].

Arrhythmogenesis and cardiac electrophysiology

Emerging evidence suggests that PVAT may influence cardiac electrophysiology and contribute to arrhythmogenesis through several mechanisms.

Electrical remodeling

PVAT-derived factors can influence the electrophysiological properties of cardiac myocytes, altering action potential duration, conduction velocity, and refractoriness [119–122]. Dysfunctional PVAT may promote electrical remodeling within the myocardium, predisposing to arrhythmias [119, 120, 123–125]. More research is necessary to unravel the differences between epicardial and PVAT in this field given the technical limitations associated.

Autonomic modulation

Sympathetic and sensory nerve fibers innervate the PVAT and WAT, albeit to different extents [126–130]. Nerve fibers were seen in the WAT and PVAT but there are regional and species differences, and a recent study revealed a dense innervation of sympathetic nerves in the AA PVAT and not in the mesenteric PVAT or WAT [131]. In coronary arteries, PVAT may interact with the cardiac autonomic nervous system [132, 133], although this has not been previously demonstrated. PVAT is a lipid reservoir providing energy to cardiomyocytes while also insulating the autonomic ganglia and nerve fibers. Dysregulated sympathetic activation in PVAT may lead to cardiac electrical instability and arrhythmias through effects on myocardial excitability and conduction [119, 120, 123, 125].

Inflammatory and fibrotic signaling

Inflammatory mediators released from dysfunctional PVAT can promote myocardial inflammation and fibrosis, creating a substrate for reentrant arrhythmias and conduction abnormalities [134]. Inflammatory cytokines (such as resistin) and fibrotic remodeling in PVAT may contribute to arrhythmogenesis [135, 136] in conditions such as atrial fibrillation and ventricular tachyarrhythmias [134]. PVAT has paracrine properties and functions by releasing oxidative and inflammatory stress modulators. The inflammatory response is thought to cause localized damage to the cardiac conduction system [137]. Recent results from the AMI-PROTECT trial suggest that utilizing sodium-glucose cotransporter-2 (SGLT-2) inhibitors in the perioperative phase of myocardial infarction may lower the inflammatory response and the risk of arrhythmias [138].

More studies are necessary to discriminate between the role of PVAT and epicardial fat using, for instance, a novel imaging criterion for perivascular fat inflammation: the CT FAI [11]. Transcriptome, metabolic, and phenotypic alterations in perivascular fat are reflected in FAI. It is necessary to conduct more research assessing the FAI assessment of regional epicardial adipose tissue depots, such as peri-atrial and pericoronary adipose tissue. To enhance the evaluation of PVAT physiology and pathophysiology, artificial intelligence and radiomic analysis could be used to process and expound on images [139].

In summary, PVAT is intricately involved in the pathogenesis of cardiovascular diseases, including atherosclerosis, hypertension, and arrhythmogenesis, through its effects on vascular inflammation, endothelial dysfunction, vascular tone regulation, and cardiac electrophysiology. Targeting PVAT dysfunction represents a promising therapeutic approach for mitigating cardiovascular risk and improving patient outcomes in these conditions.

Therapeutic targets and interventions for modulating PVAT function

Addressing PVAT dysfunction represents a promising approach for the prevention and treatment of cardiovascular diseases. Various therapeutic strategies aim to modulate PVAT function and mitigate its adverse effects on vascular health. These approaches include novel molecular mechanisms regulating de novo lipogenesis and carotenoid metabolism [140], pharmacological interventions that accelerate BAT metabolism by stimulating thermogenesis [141], browning of WAT [142], improving adipocyte secretory profile [143], and regulating fatty acid release and signaling [144].

Strategies aimed at modulating PVAT inflammation, restoring adipokine balance, and attenuating immune cell activation hold promise for mitigating metabolic-related vascular complications [145–147]. Lifestyle interventions, pharmacological agents targeting inflammatory pathways, and surgical approaches aimed at reducing PVAT mass or improving adipose tissue function represent potential therapeutic avenues for managing vascular diseases associated with obesity and PVAT dysfunction. Here, we explore three key therapeutic modalities targeting PVAT function: lifestyle interventions, pharmacological approaches, and surgical or interventional strategies.

Lifestyle interventions

Dietary modification

Dietary interventions focused on reducing caloric intake, improving nutrient quality, and promoting weight loss can positively impact PVAT function [63]. A diet rich in fruits, vegetables, whole grains, and lean proteins, while low in saturated fats, refined carbohydrates, and added sugars, may help to improve adipose tissue health and reduce inflammation in PVAT [63, 148]. Recent research has demonstrated that oral supplementation with sodium butyrate or beta-glucan (fiber) can mitigate the deleterious effects of a HFD, including excessive weight gain [149]. Additionally, beta-glucan changes the gut microbiome profile and diversity, while sodium butyrate causes depot-dependent changes in the chemical composition of adipose tissue [149]. Additionally, calorie restriction and intermittent fasting regimens have been shown to promote metabolic health and reduce adipose tissue inflammation [150, 151].

Regular exercise

Physical activity has profound effects on adipose tissue metabolism and function, including PVAT [152]. Regular exercise promotes adipose tissue remodeling, increases insulin sensitivity, and reduces inflammation in PVAT [117, 152–154]. Both aerobic exercise and resistance training have been shown to improve PVAT function and attenuate cardiovascular risk factors associated with obesity and metabolic syndrome [59, 83, 155–157]. Incorporating a combination of aerobic and resistance exercises into a comprehensive exercise program can optimize cardiovascular health and mitigate PVAT dysfunction.

Pharmacological approaches targeting PVAT

Anti-inflammatory agents

Pharmacological agents targeting inflammation in PVAT represent potential therapeutic interventions for cardiovascular diseases [147]. Anti-inflammatory drugs such as nonsteroidal anti-inflammatory drugs may attenuate PVAT inflammation and improve vascular function. Additionally, inhibitors of specific inflammatory pathways, such as TNFα antagonists or IL1β inhibitors, may mitigate PVAT-mediated inflammation and reduce cardiovascular risk [158].

Metabolic modulators

Drugs targeting metabolic pathways involved in adipose tissue metabolism and insulin sensitivity may improve PVAT function and metabolic health. Insulin sensitizers such as metformin or thiazolidinediones may enhance insulin sensitivity in PVAT and reduce adipose tissue inflammation [159, 160]. Other metabolic modulators, including peroxisome proliferator-activated receptor agonists and AMP-activated protein kinase (AMPK) activators, may also exert beneficial effects on PVAT function and cardiovascular health. Indeed, PVAT influences the activity of AMPK [159], which in turn affects the regulation of vascular homeostasis and insulin sensitivity. By enhancing endothelial function, AMPK is a heterodimeric protein that maintains insulin sensitivity and modulates vascular homeostasis [159, 161]. Its inactivation may play a role in the pathophysiology of cardiovascular diseases and type 2 diabetes mellitus [161]. The pharmacological activation of the AMPK pathway has the potential to reverse PVAT dysfunction, thereby aiding in the prevention and treatment of metabolic and cardiovascular diseases, as dysfunctional PVAT is linked to decreased AMPK activity [159, 161].

Other than liraglutide [162], antidiabetic medications like metformin and thiazolidinediones [159, 160] may activate the AMPK pathway, promoting glucose transport and raising NO bioavailability [159]. Further, the following molecules have been linked to the improvement of PVAT function and are implicated in AMPK activation: salicylate [160], methotrexate [163], resveratrol [160], the isoflavonoid calycosin [164], diosgenin [165], and mangiferin [166]. To fully comprehend these medications' effectiveness in human PVAT, more research is necessary.

Statins

Statins have been shown to have several pleiotropic effects, some of which are responsible for the endothelial modulation of the Akt pathway and caveolin-1 expression, leading to an increment in NO production and thereby improving endothelial dysfunction [167, 168] without affecting insulin resistance [169, 170]. These effects are beneficial in reducing cardiovascular risk because they inhibit hydroxyl-methyl-glutaryl coenzyme A reductase, which induces LDL reduction [171]. Based on these findings, statins might mediate PVAT secretion of bioactive molecules involved in vascular homeostasis regulation. Atorvastatin may increase the release of PVRFs, such as H_2S [172], in male Wistar rats, by inhibiting mitochondrial oxidation thereby restoring PVAT function. More research is required to demonstrate how statins affect human PVAT.

Antidiabetic drugs

Like statins, new antidiabetic medications, particularly glucagon-like peptide 1 receptor agonists (GLP-1 RAs) and SGLT-2 inhibitors, not only lower blood sugar levels but also directly lower cardiovascular risk [173, 174]. This is achieved by enhancing endothelial cell function, lowering oxidative stress, and inflammation, all of which stop atherosclerosis from developing and progressing [175–177].

Several studies have assessed the impact of GLP-1 RAs and SGLT-2 inhibitors on dysfunctional PVAT due to its role in the development of atherosclerosis by contributing to the onset of endothelial dysfunction. GLP-1 RA liraglutide decreases PVAT inflammation in male Zucker diabetic fatty rats by inhibiting the NF-κB signaling pathway [162] and enhances endothelial dysfunction in male mice by activating the PVAT-AMPK/eNOS pathway and increasing the bioavailability of PVAT-derived adiponectin [178]. Given these results, one could hypothesize that GLP-1 RAs help lower cardiovascular risk by restoring the bioavailability of NO and adiponectin in PVAT.

Additionally, proinflammatory cytokine expression, including adhesion molecules, was found to be decreased in male ApoE−/− mice treated with the SGLT-2 inhibitor empagliflozin, as was the activity of NADPH oxidase in PVAT [179]. Therefore, by lowering PVAT inflammation and oxidative stress, empagliflozin may also prevent endothelial dysfunction and atherosclerosis in humans, in addition to animal models; however, more research is required.

Vasodilators and antihypertensive agents

Drugs that target vascular tone and blood pressure regulation may indirectly influence PVAT function and vascular health. Vasodilators such as calcium channel blockers, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, and endothelin receptor antagonists can improve endothelial function and reduce vascular resistance, potentially mitigating PVAT-mediated vascular dysfunction and hypertension [180].

Drug delivery to the periadventitial Layer

Drug delivery to the periadventitial layer is a sensible therapeutic strategy because, after balloon angioplasty or stent implantation, the drug directly distributes around the blood vessel's outer layer, causing abnormal vascular remodeling. Targeting the early stages of proinflammatory mediator release, vasa vasorum neovascularization, and resident stem/progenitor cell mobilization, which result in the formation of neointima, may have its benefits [181].

Several techniques, such as a needle-equipped microinfusion catheter and three-dimensionally printed microneedles enclosed in deflated balloon folds that puncture the vessel wall when inflated, have been developed to administer medications into the periadventitial layer [182, 183]. A wire-guided catheter with a single needle enclosed in a balloon makes up a microinfusion catheter system; when the balloon is inflated, the microneedle is released, penetrating the periadventitial layer and the external elastic lamina to release the drug [183]. However, medications are delivered into tiny vessels by microneedles inside a balloon system, necessitating repeated injections [182].

Therapies administered by microneedle or microinfusion systems create a steep concentration gradient in the periadventitial layer of inflammatory origin and disperses in the external cylindrical layer. Therefore, after endovascular procedures, neointima formation may be prevented by means of drug delivery systems directly to PVAT [183]. As an alternative, medications that promote intimal growth can be directly applied to the periadventitial layer during open surgical repair procedures like bypass grafting or arteriovenous fistula access for hemodialysis [184, 185]. For periadventitial drug delivery, numerous biomaterial systems, including nanoparticles, wraps, and bioresorbable hydrogels, have been developed [186, 187].

Nanoparticles enable drug penetration into the vessel wall and maintain fractional drug release over time in drug-loading platforms based on nanotechnological methods [188]. Compound encapsulation in hydrogel-loaded bioresorbable polymeric nanoparticles may improve local peripheral vein delivery and extend fractional drug release [189]. It has been observed that intimal hyperplasia in rat carotid arteries injured by balloons can be prevented by directly painting the periadventitial surface with drug-loaded unimolecular micelle nanoparticles [181]. An alternate strategy for securing a medication around PVAT and attaining sustained drug release is

targeted delivery of nanoencapsulated drug formulations [188].

More research is necessary to determine whether painting PVAT with drug-loaded nanoparticles during open vascular reconstruction procedures can prevent neointimal hyperplasia. To preserve the patency of endovascular implants, localized periadventitial delivery of anti-inflammatory and antiproliferative medications is a workable strategy.

Surgical and interventional strategies

Bariatric surgery

Surgical interventions such as bariatric surgery can lead to significant weight loss and metabolic improvements, including alterations in PVAT function. Bariatric procedures such as gastric bypass or sleeve gastrectomy have been shown to reduce adipose tissue inflammation, improve insulin sensitivity, and attenuate cardiovascular risk factors associated with obesity and metabolic syndrome [190]. These metabolic benefits may contribute to the amelioration of PVAT dysfunction and cardiovascular disease risk following bariatric surgery [190].

PVAT removal or modification

Emerging surgical and interventional techniques aim to directly target PVAT for therapeutic purposes. Approaches such as PVAT removal or modification, using minimally invasive or catheter-based procedures, may offer novel strategies for mitigating PVAT-mediated vascular dysfunction and cardiovascular risk. These approaches require further research to establish their safety and efficacy.

In summary, therapeutic interventions targeting PVAT function hold promise for the prevention and treatment of cardiovascular diseases. Lifestyle modifications, pharmacological agents, and surgical or interventional strategies aimed at improving PVAT health and function may provide valuable therapeutic options for individuals at risk of or affected by cardiovascular conditions associated with PVAT dysfunction. Continued research efforts are needed to optimize these interventions and elucidate their long-term effects on cardiovascular outcomes.

Emerging research in PVAT studies

PVAT research is a rapidly evolving field with ongoing advancements in understanding its role in cardiovascular health and disease. Emerging research focuses on several key areas that hold promise for advancing our understanding of PVAT biology and its implications for cardiovascular health. Here are two important areas of emerging research and future directions in PVAT studies.

Novel imaging techniques for PVAT assessment

Because of PVAT's significance in cardiometabolic disorders, there is a perpetual need for novel analytical instruments to characterize PVAT and its lipid profile noninvasively and to comprehend the mechanisms that connect PVAT to vascular function. Only a few well-established methods, such as PET, CT, MRI, and ultrasonography, have been proven effective in investigating PVAT because of its unique location and heterogeneity [10–12]. Every imaging modality has different limitations and can provide different types and amounts of information. For example, echocardiography can measure the thickness of epicardial adipose tissue but not PVAT; MRI can assess PVAT area and volume but only on large arteries; PET can provide information about uptake and tissue inflammation but requires the use of radiotracers and harmful gamma radiation; and CT can provide a FAI that describes the size and lipid content of adipocyte [10, 11] but also exposes patients to radiation. A recent review by Antoniades and colleagues [10] detailed the deeper analysis, which included cost, clinical availability, and reproducibility of different imaging modalities in assessing PVAT phenotype. Aside from a few drawbacks, CT is thought to be the best option for characterizing and visualizing PVAT. Volumetric PVAT quantification is made possible by high spatial resolution coronary Computed Tomography Angiography in vivo clinical studies, which is particularly useful in the field of vascular inflammation [11]. In patients who are at high risk of developing atherosclerotic plaques, the novel CT imaging biomarker FAI is proposed to better predict cardiac risk by capturing coronary inflammation [191]. However, this technology cannot be applied so effectively to TA PVAT or mesenteric PVAT. In addition, the attenuation of PVAT by CT scans does not provide the chemical insight of the studied tissue that can be obtained by Raman spectroscopy, even in single cells. Rather, it represents the balance between lipid and aqueous phases shifted in vascular inflammation, as well as the presence of small, less differentiated adipocytes and alterations in the lipid profile [10–12].

Magnetic resonance imaging and spectroscopy

Advanced MRI techniques, including proton density-weighted MRI, fat-water MRI, and magnetic resonance spectroscopy, offer non-invasive methods for assessing PVAT volume, composition, and metabolic activity [192–194]. These techniques provide valuable insights into PVAT characteristics and their relationship with cardiovascular risk factors and disease [10].

Computed tomography angiography

CT angiography combined with dedicated PVAT imaging protocols allows for the quantification of PVAT volume

and characterization of PVAT distribution around blood vessels. High-resolution CT imaging techniques provide detailed anatomical information and facilitate the study of PVAT dynamics in relation to vascular function and disease progression [10].

Near-infrared spectroscopy

Near-Infrared Spectroscopy (NIRS) is emerging as a promising modality for assessing PVAT oxygenation and metabolic activity. NIRS techniques enable real-time monitoring of PVAT oxygen saturation and hemodynamics, providing insights into the physiological and pathophysiological changes occurring within PVAT in response to metabolic and vascular stimuli [195, 196].

Raman spectroscopy

Conventional Raman spectroscopy enables PVAT characterization through lipid unsaturation degree, or level of triacylglycerols. Lipid unsaturation degree has been shown to function as a chemical indicator of endothelial/vascular inflammation [197, 198]. Combining optical and Raman spectroscopy to provide high spatial resolution imaging at the subcellular level, Raman microscopy allows for composition analysis and sample component distribution visualization. Butler and colleagues' review [199] provided an overview of various Raman spectroscopy-based methods as well as the advantages and disadvantages of experiments in biomedical applications.

Advancements in technology for studying PVAT in vivo [10], in vitro [14], and at the molecular level [13] have a quantifiable effect on basic research and diagnostic opportunities. Even though in vivo testing is not possible due to the location of the PVAT and the limited depth penetration of scattered light, Raman spectroscopy techniques can be used in PVAT investigation to quickly analyze the impact of the active ingredient on the chemical conversion of adipocytes [12, 200] and investigate the heterogeneity of the PVAT response in animal models [41, 112]. Studies using Raman spectroscopy may offer a new means of advancing our understanding of the pharmacology of PVAT browning, since PVAT browning or maintaining the beige phenotype of PVAT represents an approach to maintaining a healthy circulation.

Biomarkers and predictive models for PVAT-related cardiovascular risk

Biomarkers of PVAT dysfunction

Identification of circulating biomarkers associated with PVAT dysfunction holds potential for assessing cardiovascular risk and guiding therapeutic interventions. Studies are investigating novel biomarkers, such as adipokines, cytokines, and microRNAs, as indicators of PVAT health and predictors of cardiovascular outcomes [10].

Predictive models and risk stratification

Development of predictive models and risk stratification algorithms incorporating PVAT-related variables may enhance cardiovascular risk assessment and personalized medicine approaches. Integrating PVAT imaging data, molecular biomarkers, and clinical parameters into predictive models enables more accurate risk stratification and targeted interventions for individuals at heightened cardiovascular risk [10].

Machine learning and artificial intelligence

Application of machine learning and artificial intelligence techniques to large-scale datasets facilitates the discovery of novel associations and predictive patterns related to PVAT function and cardiovascular outcomes [201]. Advanced computational approaches enable the development of predictive models that can leverage diverse data sources to optimize risk prediction and inform clinical decision-making.

In summary, emerging research in PVAT studies is focused on advancing our understanding of PVAT biology, developing innovative imaging techniques, elucidating molecular signaling pathways, and identifying biomarkers and predictive models for assessing cardiovascular risk [10]. These efforts hold promise for uncovering new therapeutic targets and improving risk stratification strategies for individuals at risk of or affected by cardiovascular diseases associated with PVAT dysfunction. Continued interdisciplinary collaboration and technological innovation are essential for driving forward progress in PVAT research and translating findings into clinical practice.

Clinical implications and translational perspectives

PVAT has emerged as a critical player in cardiovascular health and disease, with implications ranging from vascular function to metabolic regulation. PVAT also contributes to whole-body thermogenesis and protects against atherosclerosis. Currently, the majority of PVAT research conducted in human clinical studies focuses on metabolic and cardiovascular disorders, such as atherosclerosis [11], aortic aneurysm [202], obesity, diabetes [54] and peripheral artery disease [115, 203]. Integrating PVAT knowledge into clinical practice holds promise for advancing cardiovascular management and improving patient outcomes. For instance, PVAT has an important protective role against vascular injury and dysfunction, with slower progression of atherosclerosis in vein grafts harvested with 'no touch' technique compared with conventional harvesting technique in coronary artery bypass grafting [10, 44, 134].

The phenotype of internal thoracic artery (ITA) PVAT has been investigated in several human studies [204–206]. Although a previous study found that the human

ITA PVAT had a white phenotype, it's vital to remember that 84% of the participants were overweight or obese, which may have had an impact on how their adipose tissue phenotype [204]. However, the contractile response to phenylephrine and U46619 (an agonist of thromboxane A2/prostaglandin H2 receptor) was attenuated by PVAT of human ITA, a vessel resistant to atherosclerosis [204]. Transferring PVAT-incubated supernatant to arteries stripped of PVAT produced similar results [204]. Importantly, sample acquisition challenges and the fact that human thoracic PVAT is frequently isolated from patients with cardiovascular complications undermines phenotypic assessment, making detailed analysis of the data difficult.

In a prospective study, increased vascular inflammation, as measured by PVAT density, was found to be independently linked to the development of lipid components in coronary atherosclerotic plaques [207]. Furthermore, and in close relation to the higher level of secreting phosphorylated protein 1 (SPP1) in PVAT, the percentage of PVAT fibrosis increased around coronary atherosclerosis and was positively correlated with the degree of coronary artery stenosis [38]]. By promoting the proliferation and migration of fibroblast adipocyte progenitors through OPN-CD44/integrin interactions, SPP1 + macrophages congregate in PVAT surrounding atherosclerotic coronary arteries, exacerbating the fibrosis of coronary PVAT [38]. It is noteworthy that in cardiac patients undergoing elective coronary artery bypass grafting, coronary artery PVAT exhibited higher levels of meta-inflammation and fibrosis compared to internal thoracic PVAT [86, 191]. Future research and discussion are necessary because it seems that inflammation and adipose tissue remodeling have no effect on the ITA PVAT.

Understanding the clinical implications of PVAT and translating this knowledge into practice is crucial for improving cardiovascular risk assessment and developing targeted therapeutic interventions. By leveraging PVAT as a diagnostic and prognostic marker, integrating PVAT knowledge into risk assessment algorithms, and pursuing translational opportunities for PVAT-targeted therapies, clinicians and researchers can advance the field of cardiovascular medicine and improve patient outcomes. Continued interdisciplinary collaboration and translational research efforts are essential for realizing the full potential of PVAT-based approaches in cardiovascular disease management [38].

Gaps in knowledge and future perspectives

In spite of the fact that current studies have emphasized the critical connections among obesity, adipose tissue, and vascular function, several significant questions remain. A deeper comprehension of the cellular and molecular components of PVAT as well as its developmental origin is fundamentally required. In addition, the role of exosomes and microvesicles secreted by PVAT and their effects on vascular smooth muscle cells and endothelial cells is still an emerging field. Understanding how PVAT-derived exosomes influence vascular inflammation and function could reveal new therapeutic targets. Further illuminating the ways in which excess adiposity contributes to vascular dysfunction in general and, more specifically, to the pathogenesis of diabetes, hypertension, and vascular stiffening will be a thorough characterization of the secreted peptides and metabolites released by PVAT in normal physiology and cardiometabolic diseases. In addition, there is growing evidence that men and women may have different PVAT characteristics and responses to obesity and diabetes. Investigating sex-specific mechanisms may uncover why cardiovascular diseases manifest differently in men and women. It is imperative that forthcoming research delves into the ways in which genetics, environment, epigenetics, and microbiota influence the way in which the various PVAT and the vasculature interact.

Conclusion

PVAT has become a vital regulator of vascular health and function. PVAT is more than a mere adipose tissue surrounding blood vessels; it actively regulates vascular function through the secretion of adipokines, regulation of vascular tone, and interaction with neighboring cells. Dysfunctional PVAT plays a significant role in the development of cardiovascular diseases, including atherosclerosis, hypertension, and arrhythmias, by promoting inflammation, endothelial dysfunction, and vascular remodeling.

Elucidating the molecular mechanisms governing adipokine secretion and signaling pathways in PVAT is important for understanding its role in vascular physiology and pathology. PVAT inflammation is also a critical determinant of cardiovascular risk, and research efforts are directed towards unraveling the molecular mechanisms underlying PVAT-derived inflammation. In addition, dysregulated lipid metabolism and metabolic dysfunction in PVAT associated with cardiometabolic disorders contribute to cardiovascular disease pathogenesis. Studies are exploring the molecular pathways involved in lipid storage, lipolysis, and fatty acid metabolism in PVAT, as well as their implications for vascular health and disease progression.

Integrating PVAT knowledge into holistic cardiovascular management holds immense potential for improving patient care and reducing the burden of cardiovascular disease. By leveraging multidisciplinary approaches, we can unlock new insights into PVAT biology, develop innovative diagnostic, improving cardiovascular risk assessment and therapeutic strategies, and ultimately

enhance cardiovascular outcomes for individuals worldwide. Together, we can harness the power of PVAT to revolutionize cardiovascular medicine and usher in a new era of personalized, precision healthcare.

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CS and MQ wrote the manuscript draft and designed the figures. CS revised the manuscript. Both authors approved the final version of the manuscript.

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