REVIEW

Physiology and Pathobiology of Perivascular Adipose Tissue: Inflammation-based Atherogenesis

Barbora MUFFOVÁ[1,2], Ivana KRÁLOVÁ LESNÁ[1,3], Rudolf POLEDNE[1]

[1]Atherosclerosis Research Laboratory, Experimental Medicine Center, Institute for Clinical and Experimental Medicine, Prague, Czech Republic, [2]Department of Physiology, Faculty of Science, Charles University, Prague, Czech Republic, [3]Department of Anesthesiology, Resuscitation and Intensive Care Medicine, 1st Faculty of Medicine of Charles University and Military University Hospital, Prague, Czech Republic

Received April 16, 2024
Accepted August 20, 2024

Summary

Perivascular adipose tissue (PVAT) envelops the majority of systemic vessels, providing crucial mechanical support and vessel protection. In physiological conditions, PVAT releases various bioactive molecules, contributing to the anti-inflammatory environment around neighboring vessels. However, in conditions like obesity, PVAT can exacerbate cardiovascular issues such as atherosclerosis. Communication between PVAT and nearby vessels is bidirectional, with PVAT responding dynamically to signals from the vasculature. This responsiveness positions PVAT as a promising indicator of vascular inflammation. Recently, the role of PVAT in the CVD risk prediction is also greatly discussed. The objective of this review is to summarize the current state of knowledge about the PVAT function, its role in physiologic and pathophysiologic processes and its potential in CVD risk prediction.

Keywords

Perivascular adipose tissue • inflammation • atherogenesis • Fat attenuation index

Corresponding author

Barbora Muffová, Patočkova 1422/47, 16900 Praha 6, Czech Republic. E-mail: barboramuffova@gmail.com

Introduction

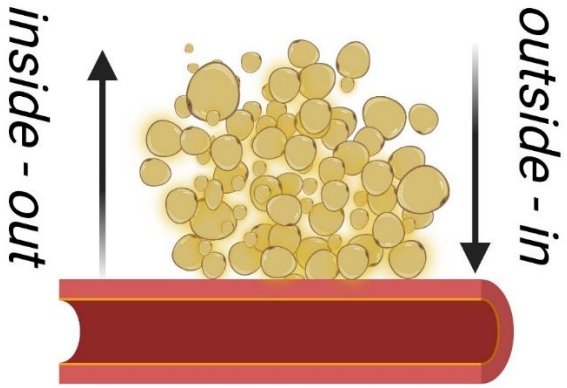
In October 2023, the longitudinal Framingham Heart Study celebrated 75 years since the first participant examination in 1948. It was the Framingham study that, as the very first project of its kind, began to elucidate the epidemiology of atherosclerotic cardiovascular disease (CVD). Since then, the study has contributed to the understanding of many aspects of atherosclerotic cardiovascular disease including the significant role of adipose tissue (AT) [1].

Adipose tissue is a connective tissue that extends throughout the body and is located under the skin as subcutaneous AT (SAT), between internal organs as visceral AT (VAT) and around the blood vessels as perivascular AT (PVAT). Originally, AT was considered to serve an insulation function to protect the body against cold [2] and as an important energy reservoir [3]. However, the impressive body of clinical and experimental data obtained over the years has thoroughly changed the picture of AT functions to finally perceive AT as a full-fledged paracrine and endocrine organ [4]. Since then, interest in AT has rapidly increased and the tissue and its signaling are being intensively studied [5].

PVAT surrounds most of the systemic vessels [6] except for the cerebral vasculature [7] and represents up to 3 % of total body mass, whereas SAT makes up 82–97 % of total fat, and VAT 10–15 % [8]. PVAT is tightly adherent to the vascular wall without a clear barrier between PVAT and the adventitia, thus it is also referred to as the fourth layer of the vessel wall (tunica adiposa) [9]. Because of the absence of a strictly defined anatomical barrier between PVAT and adjacent vessel wall, and

PVAT and neighboring AT depot, and overall inconsistence in the definitions of PVAT, Antonopoulos *et al.* recently proposed a new definition based on their results [10,11]. The authors defined PVAT as an AT depot located within the radial distance from the outer vessel wall with its amount to be equal to the diameter of the adjacent vessel. In 2010, the Framingham Heart Offspring Study, as another first, published data documenting a strong correlation between the quantity of periaortic PVAT and cardio-metabolic risk factors such as hypertension, high triglycerides levels and lower high-density lipoprotein (HDL) levels in serum. The study also identified a correlation between periaortic PVAT volume and body mass index (BMI), waist circumference (WC), and overall adiposity values. Moreover, the study authors found an association between PVAT size and calcification of the aorta and abdominal aorta [1]. Recent data have also indicated that the role of PVAT is substantially influenced by lifestyle, even in childhood [12].

Scientific interest in PVAT and its physiologic and pathologic roles has grown considerably in the past decade. In this review, we aim to overview the current knowledge and clinical prospects.



Graphical abstract 1. The inside-out and outside-in communication between vessel and adjacent perivascular adipose tissue. Created with biorender.com.

Developmental origin of PVAT adipocytes

PVAT surrounds most of the veins in the human body; however, four main subtypes have been the most extensively studied [13]: 1. Pericoronary PVAT (cPVAT), which is adjacent to heart vasculature; 2. Thoracic PVAT (tPVAT) present from the aortic arch at T4 to the T10–T11 vertebrae above the diaphragm; 3. Abdominal periaortic aPVAT from below the diaphragm to the femoral bifurcation; and 4. mPVAT surrounding the mesenteric artery. Interestingly, PVAT subtypes differ not only in their localization but show significant differences also in adipocyte morphology, developmental origin of PVAT adipocytes, gene expression, and secretome profile [13]. Thus, they also differ in function and in their involvement in metabolic disorders or CVD.

Despite progress in lineage tracing of classical AT depots, the developmental origin of PVAT remains largely unknown [14]. Numerous publications have presented a wealth of information, unfortunately inconsistent. This inconsistency may be due to the absence of a strict border between PVAT and neighboring fat depots, where one likely overlaps the other. Thus, not only is it nearly impossible to separate PVAT from nearby AT depots but, also, to subsequently identify whether the isolated adipocytes belong to PVAT; hence, it is often challenging to specify their developmental origin. However, a review article by Li *et al.* [13] briefly summarized that adipocytes of PVAT in various depots have different developmental origins. While the number of publications elucidating the cell origin of human PVAT is currently limited, animal-based studies have generated large amounts of data in this respect.

Recently, a comprehensive study using a murine model elucidated the developmental origin of tPVAT adipocytes [15]. Its authors demonstrated a most important role of a fibroblast lineage, consisting of progenitor cells and preadipocytes, transcriptionally similar to analogous cell types in WAT. In addition, the study discovered, in the aortic adventitia of adult animals, a population of adipogenic smooth muscle cells (SMC), which contribute to PVAT adipocyte formation. Similarly the authors, relying on animal studies, identified presumptive fibroblastic and SMC-like adipocyte progenitor cells in human tPVAT [15]. Overall, data from murine models indicate three different tPVAT depots around the thoracic aorta [16] with slight differences in tPVAT depots adipocyte progenitors. These findings, while indicating differences in cell lineages, also suggest different physiological and pathological functions of these depots.

Similar to tPVAT, recent data indicate that SMC progenitors play a crucial role in the development of adipocytes in aPVAT and mPVAT as well [17]. Research using rodent models has shown that aPVAT and mPVAT adipocytes express markers typical of mesenchymal precursor cells playing an important role in the development of vascular SMCs [17], suggesting an effect of vasculature progenitor cells in PVAT development.

To our best knowledge, there is currently no study focusing on the developmental origin of adipocytes in

cPVAT in human or animal models. This might be due to the lack of pericoronary and epicardial AT in rodents [18] and difficult purchase of this AT depot from humans.

PVAT cellular composition

To comprehensively understand the complexity and heterogeneous functions of PVAT depots, it is essential to delineate AT cellular composition. The majority of studies generally refer to PVAT as a mixture of white and brown adipocytes; however, PVAT composition differs significantly between various locations within the body [19], and adipocytes exhibit the characteristics of WAT, BAT or beige AT with variations observed between distinct PVAT depots [13]. While WAT adipocytes are typically characterized by large unilocular lipid droplets, fewer mitochondria and small cytoplasmic volumes, BAT adipocytes are often multilocular with a high density of mitochondria [13]. Apart from adipocytes, PVAT harbors a diverse array of cell types, which are collectively called cells of the stromal vascular fraction (SVF) comprising preadipocytes, immunocytes, fibroblasts and nerves. In the text below, we briefly summarize the cell types in the four main subtypes of PVAT.

Adipocytes

One of the very first studies considered human cPVAT a subtype of white AT (WAT) with unilocular adipocytes and gene expression more related to WAT [20]. However, Sacks *et al.*, using analysis of gene expression, suggested cPVAT to exhibit beige features [21]. cPVAT adipocytes express appreciable levels of the beige AT marker, cluster differentiation (CD) 137 and markers typical of adipocyte browning and classical brown AT (BAT) development. According to these and other authors, cPVAT adipocytes display high gene expression of uncoupling protein-1 (UCP-1), the typical brown BAT marker [21-23]. Altogether, although – morphologically – cPVAT tends to exhibit WAT characteristics, the gene expression of adipocytes clearly shows it is more related to BAT or beige AT.

Data derived recently from murine models indicate that tPVAT displays rather BAT-like features, as tPVAT adipocytes express transcription factors typical of brown adipocytes in amounts comparable to interscapular BAT [15]. Likewise, genes associated with mitochondrial biogenesis were highly expressed in tPVAT preadipocytes [15] when compared to WAT adipocytes. This is consistent with the abundant presence of mitochondria within multilocular brown adipocytes when compared to WAT-like aPVAT in rodents [24]. Interestingly, using a murine model, it has been recently demonstrated that there are three different tPVAT depots around the thoracic aorta [16], a finding clearly documenting the diversity of PVAT.

Contrarily, based on animal study data, both aPVAT and mPVAT tend to share WAT characteristics, as reviewed in Li, Ma *et al.* [13]. Adipocytes are characterized primarily as white, mostly unilocular [24-26] with few brown or beige adipocytes [25,26].

Immunocytes

Recent comprehensive analyses by Kumar *et al.* defined the roles of a wide range of immune cells present in rodent PVAT, including monocytes/macrophages, granulocytes, nature killer (NK) cells and lymphocytes, which exhibit a variety of phenotypes as well as activation and polarization states [27]. Also present in PVAT are dendritic cells (DC) [28] and innate lymphoid cells (ILC) [29].

Macrophages, the most abundant immune cells in AT [30] have also been extensively studied in PVAT [31-34]. PVAT harbors distinct macrophage subpopulations reflecting the local microenvironment and secreting numerous cytokines [32,35] that affect the local inflammatory state of PVAT and adjacent vessel wall.

Other types of cells also found in PVAT include granulocytes, eosinophils and neutrophils [36]. While eosinophils rather exert an anti-inflammatory effect on the PVAT phenotype and its physiological functions [37], neutrophil counts increase in obesity and likely contribute to PVAT dysfunctionality, at least in rodent models [38,39]. Eosinophils typically cooperate with anti-inflammatory cells such as type 2 helper T cells (Th2) or, alternatively activated, generally considered as anti-inflammatory, type 2 macrophages (M2), contributing to the overall anti-inflammatory state of PVAT [40,41].

DC are very potent antigen-presenting cells also found in PVAT, where their role has been described in the context of hypertension promotion [42] and over-production of pro-inflammatory cytokines [43] depending on the metabolic and disease status of individuals.

As with DC, the NK cell counts and activity in PVAT have been shown to be associated with hypertension in rat models [44]. Nevertheless, their role is much less clearly defined than in VAT, where NK link obesity-

induced adipose stress to inflammation and insulin resistance in part through interferon gamma (IFN-γ) release [45].

ILC have garnered considerable attention and research focus over the past decade. They are lymphocytes without the classical diversified antigen receptors, typical for T and B cells [46]. Their functions bear similarities to the conventional immune cells such as T cells or macrophages, albeit in a simplified manner. Despite their importance, ILCs have not been extensively studied in the context of PVAT. However, investigations have revealed that a specific subtype of ILCs called CD25+ type 2 ILC (ILC2) plays a role in reducing atherosclerosis in murine models [29]. Additionally, these cells regulate PVAT homeostasis by maintaining an anti-inflammatory environment through the induction of M2 macrophages and eosinophils [47].

Yet another cell type found in PVAT are immunocytes of the adaptive immune system. Piacentini *et al.* identified a diverse clonal repertoire of T lymphocytes in PVAT depots in rodents [48], with some found also in humans [49]. The authors hypothesized that the repertoire of T cells in PVAT differs between pathological conditions thus suggesting the involvement of specific antigen-specific immune responses. Besides, several phenotypes of B cells, type 1 B cells (B-1) and type 2 B cells (B-2 cells) have been detected in human PVAT. They are located in fat-associated lymphoid clusters [33,50-52] and display anti-atherogenic (B1-cells) or pro-atherogenic (B-2 cells) properties.

Other cells

In addition to the above cell types, the SVF of PVAT contains fibroblasts, pericytes and nerves. Like preadipocytes, fibroblasts have been shown to have adipogenic potential in rodent models [36]. However, their adipogenic capacity appears exclusive to adventitial fibroblasts [53], leaving the role of fibroblasts in PVAT somewhat ambiguous.

A recently identified cellular component of PVAT are pericytes [34], supporting the blood vessel formation and contraction, with function predominantly in association with the central nervous system [34,54]. And, yet another important cell type present in PVAT is the neuron (nerve cell) playing a vital role in maintaining vascular tone by secreting vasoconstrictive compounds [55,56]. Notably, an increase in the number of nerve fibers has been identified in the cPVAT of patients developing acute myocardial infarction (AMI), and found to correlate with decreased cPVAT thickness in these patients, suggesting potential involvement of nerves in PVAT dysfunctionality [56].

PVAT and vascular modulation

PVAT mechanically supports and protects the adjacent vasculature [57,58]. Vein grafts surrounded by PVAT exhibit significantly better patency and function compared to those without adjacent PVAT [59,60]. Besides, PVAT acts as a mechanical buffer shielding the graft against arterial hemodynamics [61], while also secreting adipokines that support the anti-inflammatory state of the vasculature. Finally, PVAT adipocytes influence the contractility of adjacent vasculature by secreting vasodilating molecules [38].

Metabolic activity of PVAT

As discussed earlier, various PVAT depots exhibit different AT characteristics; for instance, PVAT depots with brown or beige adipocytes possess thermogenic properties [62]. Brown adipocytes express UCP1, dissipating energy as heat through uncoupling oxidative phosphorylation from ATP production. PVAT thermogenesis contributes to energy expenditure and metabolic regulation, potentially influencing systemic energy balance and body weight [62]. Unlike WAT, BAT adipocytes have anti-inflammatory properties [17,63-65]. Browning of adipocytes can shift macrophage polarization toward the anti-inflammatory phenotype in the mouse [65], while whitening of brown adipocytes is associated with AT inflammation [63]. Similarly, beige adipocytes may also display anti-inflammatory attributes, as demonstrated by the attenuation of inflammation and pathological vascular remodeling in murine models [66]. Single-cell RNA sequencing revealed the critical regulation of alternatively activated, anti-inflammatory M2 macrophages by beige adipocytes in rodent PVAT. Interestingly, adipocyte beiging was also observed in the tPVAT of patients in acute aortic dissection models, implying that beiging occurs in human aortic PVAT during acute dissection and may regulate the local inflammatory response toward the anti-inflammatory phenotype [66] . However, a review by Li *et al.* suggested human beige cPVAT is strictly pro-inflammatory [13], relying on results from inflamed human coronary artery [67]. However, to truly elucidate the physiological functions of

PVAT depots, further studies with healthy, ideally young individuals without the inflammatory and metabolic burden are warranted.

PVAT adipocytes are potent producers of adiponectin, with gene expression the highest compared to subcutaneous or epicardial AT depots [58]. Adiponectin is the most studied adipokine of PVAT with numerous metabolic properties, as comprehensively reviewed by Sowka and Dobrzyn in 2021 [68]. Some studies suggest PVAT to have an important role in insulin sensitivity and potentially subsequent hyperglycemia and type 2 diabetes development [38]. Despite PVAT's copious adiponectin secretion, its volume may be too small to significantly influence these metabolic processes compared to other AT depots. However, given the large amounts of adiponectin secreted by PVAT adipocytes, it has been speculated that the adiponectin derived from PVAT surrounding the muscle microvasculature could substantially regulate the insulin-induced vasodilation [69], at least in experimental models. Likewise, adiponectin exerts a major anti-contractile effect of PVAT on the vessel wall [38] and is crucial for physiological blood flow [38,70].

Inflammatory and pro-atherogenic processes in PVAT

Lastly and in a way, PVAT is involved in inflammatory processes through adiponectin's anti-inflammatory activity. Adiponectin contributes to reducing the expression of pro-inflammatory cytokines such as interleukin (IL)-6 and tumor necrosis factor alfa (TNFα), probably via inhibiting the nuclear factor kappa B (NF-κB pathway) [71-73]. Conversely, adiponectin stimulates the production of anti-inflammatory cytokines such as IL-10 and IL-1RA [74,75]. Adiponectin inhibits the classical pro-inflammatory activity of M1 macrophages and enhances the anti-inflammatory activity of M2 macrophages [76]. Given PVAT's high gene expression of adiponectin [58], it likely has a crucial effect on the anti-inflammatory functions of PVAT and adjacent vasculature.

Using murine models, it has been demonstrated that chronic PVAT inflammation leads to thickening of the intima-media of the adjacent aorta via TNFα signaling [77]. Thickening of the intima-media of the vessel wall is a hallmark of vascular pathologies including atherosclerosis [77]. TNFα expression is significantly increased in patients with peripheral arterial disease (PAD) [35]. In humans, TNFα stimulates the proliferation of vascular smooth muscle cells [78], likely via NF-κB pathway signaling [79]. Thus, TNFα overexpression in PVAT [35] might also be involved in vessel wall thickening in humans. Moreover, as demonstrated in VAT, TNFα plays an important role in monocyte adhesion to the endothelium [80] as one of the very first steps in atherosclerosis development. These data, together with earlier results of Čejková *et al.* [35], highlight the significant effect of PVAT on adjacent vasculature and initiation of atherosclerosis.

Cardio-metabolic diseases are usually associated with obesity, which has multiple effects on cardiovascular structure, function, and circulation [81] and has also been shown to correlate with the risk of CVD development [82]. In obesity, immunocyte infiltration to AT is increased [83] and infiltrated immunocytes phenotypically switch towards the pro-inflammatory state [84]. Moreover, obesity contributes to AT remodeling, as reflected in adipocyte hypertrophy and hyperplasia [85,86], leading to an increase in AT volume.

Framingham study researchers identified a noteworthy correlation between the volume of cPVAT on the one hand and those of VAT and SAT as well as anthropometric measures of obesity (BMI and WC) on the other (Schlett, Massaro *et al.* 2009). Likewise, unhealthy lifestyle habits have been proven to negatively influence children's cPVAT [12] increasing as it does tissue thickness. PVAT thickness in overweight or obese children has been shown to correlate with high blood pressure and increased levels of triglycerides in serum [87] and inversely correlate with HDL cholesterol levels in serum [87]. These results are consistent with data of our team demonstrating a correlation between the adipocyte size in PVAT and body composition, as reflected in BMI and WC (Bartušková *et al.*, submitted) of healthy subjects. We also identified a correlation between adipocyte size and the proportion of metabolically activated, pro-inflammatory macrophages (Bartušková *et al.*, submitted) in healthy individuals, a finding consistent with their higher infiltration in PVAT [32].

PVAT as a biosensor of vascular inflammation

In the text above, we have summarized the main effects of PVAT on the adjacent vessel wall. The great majority of pro-inflammatory effects are related to the release of bioactive molecules that exert endocrine and paracrine atherosclerotic effects on the vascular wall.

More recently, an opposite effect was described whereas the vessel wall might influence PVAT [88], suggesting the bidirectional nature of their relationship. This inside-out and outside-in communication was reliably documented in an experimental model [66], where signals from injured vasculature induced beiging of adjacent tPVAT. The phenotypic switch of PVAT supported the anti-inflammatory processes, contributing to resolution of vascular inflammation and remodeling [66].

Perivascular Fat Attenuation Index (FAI)

Over the past decade, the concept of PVAT as a biosensor of vascular inflammation has gained traction. Cells within the inflamed vessel wall secrete pro-inflammatory molecules such as IL-6, tumor TNFα, and interferon-gamma (IFNγ), which diffuse into neighboring PVAT [10,11]. Prolonged exposure to these paracrine inflammatory signals can negatively affect the differentiation of preadipocytes into mature adipocytes, impair the intracellular accumulation of lipid droplets [10] and trigger lipolysis [11,89]. Collectively, pro-inflammatory signals from the inflamed vasculature induce morphological changes in PVAT characterized by a low lipid content and an increase in the aqueous:lipid phase balance of the tissue. This phenomenon is known as adipose tissue attenuation. It is captured by computed tomography (CT) and reaches values ranging from –190 to –30 Hounsfield units (HU) at water attenuation defined as zero HU [10,90]. Antonopoulos *et al.* have demonstrated that AT with larger adipocyte shifts the attenuation values toward –190 HU, whereas that with smaller adipocytes reaches attenuation levels closer to aquatic values of around –30 HU [10], with the implication being that fat attenuation values could be possibly employed to detect vascular inflammation. This is a basic principle of the perivascular fat attenuation index (FAI), a CT-derived, non-invasive tool to assess the balance between the lipid and water phases within PVAT [10]. Simply said, FAI visualises and quantifies impaired lipid accumulation and adipocyte differentiation in coronary artery PVAT resulting from coronary inflammation. The perivascular FAI indirectly detects vascular inflammation by mapping spatial changes within PVAT [10,11], thus reflecting the inflammatory burden of adjacent vessel wall.

Perivascular FAI in risk stratification

Pericoronary FAI serves as a measure of PVAT attenuation [91] and mirrors the ability of PVAT to function as a molecular sensor of vascular inflammation [11] regardless of the typical obesity markers such as BMI and WC.

Perivascular FAI values correlate with the burden of atherosclerotic plaques [10], with higher values indicating the presence of unstable culprit lesions [92]. However, unlike conventional CT, perivascular FAI is able to quantify vascular wall inflammation and stratify cardiovascular (CV) risk even in individuals without obstructive coronary atherosclerosis [93] and, hence, with no visible atherosclerotic plaques [94,95].

High FAI values appear to be linked to an increased risk of cardiac and all-cause death [11]. More recently, in the CaRi-Heart® study, a standardized FAI was combined with clinical risk factors and plaque metrics [96] with the ambition to easily and reliably predict the absolute risk for fatal cardiac events in individuals [96]. Additionally, Graby *et al.* suggested that FAI provides incremental value in identifying the risk of CV events, including in asymptomatic individuals without evidence of overt coronary artery disease, regardless of conventional coronary artery calcium scoring [97].

While available evidence shows that pericoronary FAI is a useful biomarker for detecting patients with high levels of vascular inflammation and for identifying vulnerable individuals at risk of CVD development, the number of studies is limited, and the relevance of FAI has been documented by only a few scientific teams to date. Contrariwise, Da *et al.* do not consider FAI a suitable prognostic tool for CVD risk stratification [98] as it was unable to demonstrate a correlation between high-risk plaque features and serum high-sensitivity C-reactive protein (hs-CRP) levels [98], generally viewed as an important marker of vascular inflammation. Moreover, even in studies showing FAI as a reliable measure of CVD risk, FAI had to be determined around strictly defined areas of coronary arteries; the proximal right coronary artery and left anterior descending artery [11] to demonstrate predictive values, with notable differences in FAI values between distinct areas [99]. Interestingly, in contrast to the right coronary artery and left anterior descending artery, FAI values are not representative for the left circumflex artery [11].

Validation of all findings is necessary to standardize FAI measurements and potentially utilize them in the assessment of vascular inflammation and risk prediction; however, classical risk markers appear to be more robust and reliable than FAI alone. Interestingly,

Antoniades, Patel *et al.* concluded that an artificial intelligence (AI)-assisted FAI score could eventually replace current prognostic models based solely on clinical risk factors [100], as it extracts information from medical images more sensitively than human operators. Could our near future unite classical approaches in CVD risk assessment with AI assistance?

Conclusion

In conclusion, according to the World Health Organization (WHO), cardiovascular disease remains one of the most common causes of death worldwide. It is no wonder then that early stratification of CVD risk remains a priority.

The nascent field of PVAT research has highlighted its pivotal role as a sensor of vascular inflammation and cardiovascular pathology. It also offers novel insights into CVD pathogenesis and PVAT's potential utility in CVD risk stratification. Through complex bidirectional communication with adjacent vasculature, PVAT dynamically responds to pro-inflammatory as well as anti-inflammatory signals, causing a wide spectrum of phenotypical changes that influence vascular health and disease. The heterogeneity of PVAT depots, characterized by distinct adipocyte phenotypes and cellular compositions, underscores the complexity of its physiological functions and pathological roles.

Imaging techniques such as perivascular FAI might usher in a new era in non-invasive CVD risk assessment. It could provide clinicians with a powerful tool to assess the inflammatory burden of the vascular wall, especially when combined with AI and conventional CVD risk factors. However, it is crucial to confirm its efficacy through comprehensive studies conducted by independent teams before its implementation in clinical practice.

In summary, although PVAT represents a dynamic and complex AT depot with far-reaching implications for cardiovascular health and disease, significant gaps remain in our understanding of PVAT biology. Future research should focus on identifying the molecular mechanisms underlying the interplay between PVAT and adjacent vasculature on and unraveling the mechanisms of PVAT dysfunction in CVD. It is an opportune time to translate preclinical findings into clinical practice, bridging various disciplines and incorporating novel technological techniques to fully utilize the potential of PVAT in improving CVD risk stratification.

Conflict of Interest

There is no conflict of interest.

Acknowledgements

Financially supported by the project (Ministry of Health, Czech Republic) for development of research organization 00023001 (Institute for Clinical and Experimental Medicine, Prague, Czech Republic) – institutional support.

References

1. Lehman SJ, Massaro JM, Schlett CL, O'Donnell CJ, Hoffmann U, Fox CS. Peri-aortic fat, cardiovascular disease risk factors, and aortic calcification: the Framingham Heart Study. Atherosclerosis 2010;210:656-661. https://doi.org/10.1016/j.atherosclerosis.2010.01.007
2. Jéquier E, Gygax P-H, Pittet P, Vannotti A. Increased thermal body insulation: relationship to the development of obesity. J Appl Physiol 1974;36:674-678. https://doi.org/10.1152/jappl.1974.36.6.674
3. Sethi JK, Vidal-Puig AJ. Thematic review series: adipocyte biology. Adipose tissue function and plasticity orchestrate nutritional adaptation. J Lipid Res 2007;48:1253-1262. https://doi.org/10.1194/jlr.R700005-JLR200
4. Pogodziński D, Ostrowska L, Smarkusz-Zarzecka J, Zyśk B. Secretome of adipose tissue as the key to understanding the endocrine function of adipose tissue. Int J Mol Sci 2022;23:2309. https://doi.org/10.3390/ijms23042309
5. Poledne R, Lesna IK, Čejková S. Adipose tissue and atherosclerosis. Physiol Res 2015;64. https://doi.org/10.33549/physiolres.933152
6. Gao Y-J. Dual modulation of vascular function by perivascular adipose tissue and its potential correlation with adiposity/lipoatrophy-related vascular dysfunction. Curr Pharm Des 2007;13:2185-2192. https://doi.org/10.2174/138161207781039634

7. Szasz T, Webb RC. Perivascular adipose tissue: more than just structural support. Clin Sci 2012;122:1-12. https://doi.org/10.1042/CS20110151
8. Siegel-Axel D, Häring H. Perivascular adipose tissue: an unique fat compartment relevant for the cardiometabolic syndrome. Rev Endocr Metab Disord 2016;17:51-60. https://doi.org/10.1007/s11154-016-9346-3
9. Chaldakov GN, Beltowsky J, Ghenev PI, Fiore M, Panayotov P, Rančič G, Aloe L. Adipoparacrinology-vascular periadventitial adipose tissue (tunica adiposa) as an example. Cell Biol Int 2012;36:327-330. https://doi.org/10.1042/CBI20110422
10. Antonopoulos AS, Sanna F, Sabharwal N, Thomas S, Oikonomou EK, Herdman L, Margaritis M, Shirodaria C, Kampoli A-M, Akoumianakis I. Detecting human coronary inflammation by imaging perivascular fat. Sci Transl Med 2017;9:eaal2658. https://doi.org/10.1126/scitranslmed.aal2658
11. Oikonomou EK, Marwan M, Desai MY, Mancio J, Alashi A, Centeno EH, Thomas S, Herdman L, Kotanidis CP, Thomas KE. Non-invasive detection of coronary inflammation using computed tomography and prediction of residual cardiovascular risk (the CRISP CT study): a post-hoc analysis of prospective outcome data. The Lancet 2018;392:929-939. https://doi.org/10.1016/S0140-6736(18)31114-0
12. Calcaterra V, Cena H, Garella V, Loperfido F, Chillemi C, Manuelli M, Mannarino S, Zuccotti G. Assessment of epicardial fat in children: its role as a cardiovascular risk factor and how it is influenced by lifestyle habits. Nutrients 2024;16:420. https://doi.org/10.3390/nu16030420
13. Li X, Ma Z, Zhu YZ. Regional heterogeneity of perivascular adipose tissue: morphology, origin, and secretome. Front Pharmacol 2021;12:697720. https://doi.org/10.3389/fphar.2021.697720
14. Sanchez-Gurmaches J, Guertin DA. Adipocyte lineages: tracing back the origins of fat. Biochim Biophys Acta Mol Basis Dis. 2014;1842:340-351. https://doi.org/10.1016/j.bbadis.2013.05.027
15. Angueira AR, Sakers AP, Holman CD, Cheng L, Arbocco MN, Shamsi F, Lynes MD, Shrestha R, Okada C, Batmanov K. Defining the lineage of thermogenic perivascular adipose tissue. Nat Metab 2021;3:469-484. https://doi.org/10.1038/s42255-021-00380-0
16. Ye M, Ruan C-C, Fu M, Xu L, Chen D, Zhu M, Zhu D, Gao P. Developmental and functional characteristics of the thoracic aorta perivascular adipocyte. Cell Mol Life Sci 2019;76:777-789. https://doi.org/10.1007/s00018-018-2970-1
17. Chang L, Villacorta L, Li R, Hamblin M, Xu W, Dou C, Zhang J, Wu J, Zeng R, Chen YE. Loss of perivascular adipose tissue on peroxisome proliferator-activated receptor-γ deletion in smooth muscle cells impairs intravascular thermoregulation and enhances atherosclerosis. Circulation 2012;126:1067-1078. https://doi.org/10.1161/CIRCULATIONAHA.112.104489
18. Shi K, Anmin R, Cai J, Qi Y, Han W, Li M, Zhang G, Zhang S, Fu L, Han W. Ascending aortic perivascular adipose tissue inflammation associates with aortic valve disease. J Cardiol 2022;80:240-248. https://doi.org/10.1016/j.jjcc.2022.04.004
19. Gruzdeva O, Borodkina D, Uchasova E, Dyleva Y, Barbarash O. Localization of fat depots and cardiovascular risk. Lipids Health Dis 2018;17:1-9. https://doi.org/10.1186/s12944-018-0856-8
20. Chatterjee TK, Stoll LL, Denning GM, Harrelson A, Blomkalns AL, Idelman G, Rothenberg FG, Neltner B, Romig-Martin SA, Dickson EW. Proinflammatory phenotype of perivascular adipocytes: influence of high-fat feeding. Circ Res 2009;104:541-549. https://doi.org/10.1161/CIRCRESAHA.108.182998
21. Sacks HS, Fain JN, Bahouth SW, Ojha S, Frontini A, Budge H, Cinti S, Symonds ME. Adult epicardial fat exhibits beige features. J Clin Endocrinol Metab 2013;98:E1448-E1455. https://doi.org/10.1210/jc.2013-1265
22. Sacks H, Symonds ME. Anatomical locations of human brown adipose tissue: functional relevance and implications in obesity and type 2 diabetes. Diabetes 2013;62:1783-1790. https://doi.org/10.2337/db12-1430
23. Chechi K, Voisine P, Mathieu P, Laplante M, Bonnet S, Picard F, Joubert P, Richard D. Functional characterization of the Ucp1-associated oxidative phenotype of human epicardial adipose tissue. Sci Rep 2017;7:15566. https://doi.org/10.1038/s41598-017-15501-7
24. Padilla J, Jenkins NT, Vieira-Potter VJ, Laughlin MH. Divergent phenotype of rat thoracic and abdominal perivascular adipose tissues. Am J Physiol Regul Integr Comp Physiol 2013;304:R543-R552. https://doi.org/10.1152/ajpregu.00567.2012

25. Police SB, Thatcher SE, Charnigo R, Daugherty A, Cassis LA. Obesity promotes inflammation in periaortic adipose tissue and angiotensin II-induced abdominal aortic aneurysm formation. Arterioscler Thromb Vasc Biol 2009;29:1458-1464. https://doi.org/10.1161/ATVBAHA.109.192658
26. Watts SW, Shaw S, Burnett R, Dorrance AM. Indoleamine 2, 3-diooxygenase in periaortic fat: mechanisms of inhibition of contraction. Am J Physiol Heart Circ Physiol 2011;301:H1236-H1247. https://doi.org/10.1152/ajpheart.00384.2011
27. Kumar RK, Jin Y, Watts SW, Rockwell CE. Naïve, regulatory, activated, and memory immune cells Co-exist in PVATs that are comparable in density to non-PVAT fats in health. Front Physiol 2020;11:58. https://doi.org/10.3389/fphys.2020.00058
28. Nosalski R, Guzik TJ. Perivascular adipose tissue inflammation in vascular disease. Br J of Pharmacol 2017;174:3496-3513. https://doi.org/10.1111/bph.13705
29. Engelbertsen D, Foks AC, Alberts-Grill N, Kuperwaser F, Chen T, Lederer JA, Jarolim P, Grabie N, Lichtman AH. Expansion of CD25+ innate lymphoid cells reduces atherosclerosis. Arterioscler Thromb Vasc Biol 2015;35:2526-2535. https://doi.org/10.1161/ATVBAHA.115.306048
30. Guzik TJ, Skiba DS, Touyz RM, Harrison DG. The role of infiltrating immune cells in dysfunctional adipose tissue. Cardiovasc Res 2017;113:1009-1023. https://doi.org/10.1093/cvr/cvx108
31. Kralova Lesna I, Petras M, Cejkova S, Kralova A, Fronek J, Janousek L, Thieme F, Tyll T, Poledne R. Cardiovascular disease predictors and adipose tissue macrophage polarization: Is there a link? Eur J Prev Cardiol 2018;25:328-334. https://doi.org/10.1177/2047487317743355
32. Kralova Lesna I, Kralova A, Cejkova S, Fronek J, Petras M, Sekerkova A, Thieme F, Janousek L, Poledne R. Characterisation and comparison of adipose tissue macrophages from human subcutaneous, visceral and perivascular adipose tissue. J Transl Med 2016;14:1-9. https://doi.org/10.1186/s12967-016-0962-1
33. Farias-Itao DS, Pasqualucci CA, Nishizawa A, da Silva LFF, Campos FM, Bittencourt MS, da Silva KCS, Leite REP, Grinberg LT, Ferretti-Rebustini REdL. B lymphocytes and macrophages in the perivascular adipose tissue are associated with coronary atherosclerosis: an autopsy study. J Am Heart Assoc 2019;8:e013793. https://doi.org/10.1161/JAHA.119.013793
34. Fu M, Shu S, Peng Z, Liu X, Chen X, Zeng Z, Yang Y, Cui H, Zhao R, Wang X. Single-Cell RNA sequencing of coronary perivascular adipose tissue from end-stage heart failure patients identifies SPP1+ macrophage subpopulation as a target for alleviating fibrosis. Arterioscler Thromb Vasc Biol 2023;43:2143-2164. https://doi.org/10.1161/ATVBAHA.123.319828
35. Čejková S, Lesná IK, Froněk J, Janoušek L, Králová A, Ždychová J, Poledne R. Pro-inflammatory gene expression in adipose tissue of patients with atherosclerosis. Physiol Res 2017;66:633-640. https://doi.org/10.33549/physiolres.933352
36. Hillock-Watling C, Gotlieb AI. The pathobiology of perivascular adipose tissue (PVAT), the fourth layer of the blood vessel wall. Cardiovasc Pathol 2022:107459. https://doi.org/10.1016/j.carpath.2022.107459
37. Withers SB, Forman R, Meza-Perez S, Sorobetea D, Sitnik K, Hopwood T, Lawrence CB, Agace WW, Else KJ, Heagerty AM. Eosinophils are key regulators of perivascular adipose tissue and vascular functionality. Sci Rep 2017;7:44571. https://doi.org/10.1038/srep44571
38. Saxton SN, Withers SB, Heagerty AM. Emerging roles of sympathetic nerves and inflammation in perivascular adipose tissue. Cardiovasc Drugs Ther 2019;33:245-259. https://doi.org/10.1007/s10557-019-06862-4
39. Costa RM, Neves K, Lopes R, Alves J, Fedoce A, Silva J, Rodrigues D, Prado D, Schnaider A, Cunha F. Neutrophil extracellular traps contribute to perivascular adipose tissue dysfunction in high‐fat diet obese mice. FASEB J 2022;36. https://doi.org/10.1096/fasebj.2022.36.S1.R4984
40. Shah K, Ignacio A, McCoy KD, Harris NL. The emerging roles of eosinophils in mucosal homeostasis. Mucosal immunol 2020;13:574-583. https://doi.org/10.1038/s41385-020-0281-y
41. Vohralik EJ, Psaila AM, Knights AJ, Quinlan KG. EoTHINophils: eosinophils as key players in adipose tissue homeostasis. Clin Exp Pharmacol Physiol 2020;47:1495-1505. https://doi.org/10.1111/1440-1681.13304
42. Kirabo A, Fontana V, De Faria AP, Loperena R, Galindo CL, Wu J, Bikineyeva AT, Dikalov S, Xiao L, Chen W. DC isoketal-modified proteins activate T cells and promote hypertension. J Clin Invest 2014;124:4642-4656. https://doi.org/10.1172/JCI74084

43. Qiu T, Li M, Tanner MA, Yang Y, Sowers JR, Korthuis RJ, Hill MA. Depletion of dendritic cells in perivascular adipose tissue improves arterial relaxation responses in type 2 diabetic mice. Metabolism 2018;85:76-89. https://doi.org/10.1016/j.metabol.2018.03.002
44. Nosalski R, Mikolajczyk T, Siedlinski M, Saju B, Koziol J, Maffia P, Guzik T. Nox1/4 inhibition exacerbates age dependent perivascular inflammation and fibrosis in a model of spontaneous hypertension. Pharmacol Res 2020;161:105235. https://doi.org/10.1016/j.phrs.2020.105235
45. Wensveen FM, Jelenčić V, Valentić S, Šestan M, Wensveen TT, Theurich S, Glasner A, Mendrila D, Štimac D, Wunderlich FT. NK cells link obesity-induced adipose stress to inflammation and insulin resistance. Nat immunol 2015;16:376-385. https://doi.org/10.1038/ni.3120
46. Vivier E, Artis D, Colonna M, Diefenbach A, Di Santo JP, Eberl G, Koyasu S, Locksley RM, McKenzie AN, Mebius RE. Innate lymphoid cells: 10 years on. Cell 2018;174:1054-1066. https://doi.org/10.1016/j.cell.2018.07.017
47. Kral M, van der Vorst EP, Surnov A, Weber C, Döring Y. ILC2-mediated immune crosstalk in chronic (vascular) inflammation. Front Immunol 2023;14:1326440. https://doi.org/10.3389/fimmu.2023.1326440
48. Piacentini L, Vavassori C, Werba PJe, Saccu C, Spirito R, Colombo GI. Deciphering abdominal aortic diseases through T-cell clonal repertoire of perivascular adipose tissue. bioRxiv 2023:2023.2012. 2005.570098. https://doi.org/10.1101/2023.12.05.570098
49. Sagan A, Mikolajczyk TP, Mrowiecki W, MacRitchie N, Daly K, Meldrum A, Migliarino S, Delles C, Urbanski K, Filip G. T cells are dominant population in human abdominal aortic aneurysms and their infiltration in the perivascular tissue correlates with disease severity. Front Immunol 2019;10:1979. https://doi.org/10.3389/fimmu.2019.01979
50. Srikakulapu P, McNamara CA. B lymphocytes and adipose tissue inflammation. Arterioscler Thromb Vasc Biol 2020;40:1110-1122. https://doi.org/10.1161/ATVBAHA.119.312467
51. Srikakulapu P, Upadhye A, Rosenfeld SM, Marshall MA, McSkimming C, Hickman AW, Mauldin IS, Ailawadi G, Lopes MBS, Taylor AM. Perivascular adipose tissue harbors atheroprotective IgM-producing B cells. Front Physiol 2017;8:719. https://doi.org/10.3389/fphys.2017.00719
52. Farias-Itao DS, Pasqualucci CA, Andrade RA, Da Silva LFF, Estevam MY, Campo AB, Suemoto CK. Increased Ratio of B2/B1-like Lymphocytes in the Perivascular Adipose Tissue Could Contribute to Plaque Destabilization in Human Coronary Arteries: Preliminary Results. Circulation 2021;144:A9162-A9162. https://doi.org/10.1161/circ.144.suppl_1.9162
53. Cattaneo P, Mukherjee D, Spinozzi S, Zhang L, Larcher V, Stallcup WB, Kataoka H, Chen J, Dimmeler S, Evans SM. Parallel lineage-tracing studies establish fibroblasts as the prevailing in vivo adipocyte progenitor. Cell Rep 2020;30:571-582. e572. https://doi.org/10.1016/j.celrep.2019.12.046
54. Attwell D, Mishra A, Hall CN, O'Farrell FM, Dalkara T. What is a pericyte? J Cereb Blood Flow Metab 2016;36:451-455. https://doi.org/10.1177/0271678X15610340
55. Shi N, Xia J, Wang C, Zhou J, Huang J, Hu M, Liao J. Aerobic exercise prevents arterial stiffness and attenuates hyperexcitation of sympathetic nerves in perivascular adipose tissue of mice after transverse aortic constriction. Int J Mol Sci 2022;23:11189. https://doi.org/10.3390/ijms231911189
56. Fiet MD, Azouz B, Robbers LF, Niessen HW, Krijnen PA. Increased epicardial nerves and decreased intramyocardial PVAT in acute myocardial infarction. Eur J Clin Invest 2023;53:e14057. https://doi.org/10.1111/eci.14057
57. Leandro A, Queiroz M, Azul L, Seiça R, Sena CM. Omentin: A novel therapeutic approach for the treatment of endothelial dysfunction in type 2 diabetes. Free Radic Biol Med 2021;162:233-242. https://doi.org/10.1016/j.freeradbiomed.2020.10.021
58. Gruzdeva OV, Dyleva YA, Belik EV, Sinitsky MY, Stasev AN, Kokov AN, Brel NK, Krivkina EO, Bychkova EE, Tarasov RS. Relationship between epicardial and coronary adipose tissue and the expression of adiponectin, leptin, and interleukin 6 in patients with coronary artery disease. J Pers Med 2022;12:129. https://doi.org/10.3390/jpm12020129

59. Souza DS, Dashwood MR, Tsui JC, Filbey D, Bodin L, Johansson B, Borowiec J. Improved patency in vein grafts harvested with surrounding tissue: results of a randomized study using three harvesting techniques. Ann Thorac Surg 2002;73:1189-1195. https://doi.org/10.1016/S0003-4975(02)03425-2
60. Samano N, Geijer H, Liden M, Fremes S, Bodin L, Souza D. The no-touch saphenous vein for coronary artery bypass grafting maintains a patency, after 16 years, comparable to the left internal thoracic artery: a randomized trial. J Thorac Cardiovasc Surg 2015;150:880-888. https://doi.org/10.1016/j.jtcvs.2015.07.027
61. Fernandez-Alfonso MS, Souza DS, Dreifaldt M, R Dashwood M. Commentary: perivascular fat and improved vein graft patency in patients undergoing coronary artery bypass surgery. Curr Vasc Pharmacol 2016;14:308-312. https://doi.org/10.2174/1570161114666160513150444
62. Szasz T, Bomfim GF, Webb RC. The influence of perivascular adipose tissue on vascular homeostasis. Vasc Health Risk Manag 2013:105-116. https://doi.org/10.2147/VHRM.S33760
63. Kotzbeck P, Giordano A, Mondini E, Murano I, Severi I, Venema W, Cecchini MP, Kershaw EE, Barbatelli G, Haemmerle G. Brown adipose tissue whitening leads to brown adipocyte death and adipose tissue inflammation [S]. J Lipid Res 2018;59:784-794. https://doi.org/10.1194/jlr.M079665
64. Xiong W, Zhao X, Villacorta L, Rom O, Garcia-Barrio MT, Guo Y, Fan Y, Zhu T, Zhang J, Zeng R. Brown adipocyte specific PPARγ deletion impairs PVAT development and enhances atherosclerosis in mice. Arterioscler Thromb Vasc Biol 2018;38:1738. https://doi.org/10.1161/ATVBAHA.118.311367
65. Zhang W-C, Qin F, Wang X-J, Liu Z-F, Zhu L, Zeng A, Zhang M-Z, Yu N-Z, Long X. Adipose-derived stromal cells attenuate adipose inflammation in obesity through adipocyte browning and polarization of M2 macrophages. Mediators Inflamm 2019;2019. https://doi.org/10.1155/2019/1731540
66. Adachi Y, Ueda K, Nomura S, Ito K, Katoh M, Katagiri M, Yamada S, Hashimoto M, Zhai B, Numata G. Beiging of perivascular adipose tissue regulates its inflammation and vascular remodeling. Nat Commun 2022;13:5117. https://doi.org/10.1038/s41467-022-32658-6
67. Numaguchi R, Furuhashi M, Matsumoto M, Sato H, Yanase Y, Kuroda Y, Harada R, Ito T, Higashiura Y, Koyama M. Differential phenotypes in perivascular adipose tissue surrounding the internal thoracic artery and diseased coronary artery. J Am Heart Assoc 2019;8:e011147. https://doi.org/10.1161/JAHA.118.011147
68. Sowka A, Dobrzyn P. Role of perivascular adipose tissue-derived adiponectin in vascular homeostasis. Cells 2021;10:1485. https://doi.org/10.3390/cells10061485
69. Turaihi AH, Serné EH, Molthoff CF, Koning JJ, Knol J, Niessen HW, Goumans MJT, van Poelgeest EM, Yudkin JS, Smulders YM. Perivascular adipose tissue controls insulin-stimulated perfusion, mitochondrial protein expression, and glucose uptake in muscle through adipomuscular arterioles. Diabetes 2020;69:603-613. https://doi.org/10.2337/db18-1066
70. Nóbrega N, Araújo NF, Reis D, Facine LM, Miranda CAS, Mota GC, Aires RD, Capettini LdSA, dos Santos Cruz J, Bonaventura D. Hydrogen peroxide and nitric oxide induce anticontractile effect of perivascular adipose tissue via renin angiotensin system activation. Nitric Oxide 2019;84:50-59. https://doi.org/10.1016/j.niox.2018.12.011
71. Ajuwon KM, Spurlock ME. Adiponectin inhibits LPS-induced NF-κB activation and IL-6 production and increases PPARγ2 expression in adipocytes. Am J Physiol Regul Integr Comp Physiol 2005;288:R1220-R1225. https://doi.org/10.1152/ajpregu.00397.2004
72. Febriza A, Ridwan R, As' ad S, Kasim VN, Idrus HH. Adiponectin and its role in inflammatory process of obesity. Mol Cell Biomed Sci 2019;3:60-66. https://doi.org/10.21705/mcbs.v3i2.66
73. Bushra S, Al-Sadeq DW, Bari R, Sahara A, Fadel A, Rizk N. Adiponectin ameliorates hyperglycemia-induced retinal endothelial dysfunction, highlighting pathways, regulators, and networks. J Inflamm Res 2022:3135-3166. https://doi.org/10.2147/JIR.S358594
74. Wolf AM, Wolf D, Rumpold H, Enrich B, Tilg H. Adiponectin induces the anti-inflammatory cytokines IL-10 and IL-1RA in human leukocytes. Biochem Biophys Res Commun 2004;323:630-635. https://doi.org/10.1016/j.bbrc.2004.08.145
75. Gruzdeva O, Akbasheva O, Dyleva YA, Antonova L, Matveeva V, Uchasova E, Fanaskova E, Karetnikova V, Ivanov S, Barbarash O. Adipokine and cytokine profiles of epicardial and subcutaneous adipose tissue in patients with coronary heart disease. Bull Exp Biol Med 2017;163:608-611. https://doi.org/10.1007/s10517-017-3860-5

76. Mandal P, Pratt BT, Barnes M, McMullen MR, Nagy LE. Molecular mechanism for adiponectin-dependent M2 macrophage polarization: link between the metabolic and innate immune activity of full-length adiponectin. J Biol Chem 2011;286:13460-13469. https://doi.org/10.1074/jbc.M110.204644
77. Moe KT, Naylynn TM, Yin NO, Khairunnisa K, Allen JC, Wong MC, Chin-Dusting J, Wong P. Tumor necrosis factor-α induces aortic intima-media thickening via perivascular adipose tissue inflammation. J Vasc Res 2013;50:228-237. https://doi.org/10.1159/000350542
78. Davis R, Pillai S, Lawrence N, Chellappan SP. TNF-α-mediated proliferation of vascular smooth muscle cells involves Raf-1-mediated inactivation of Rb and transcription of E2F1-regulated genes. Cell Cycle 2012;11:109-118. https://doi.org/10.4161/cc.11.1.18473
79. Selzman CH, Shames BD, McIntyre Jr RC, Banerjee A, Harken AH. The NFκB inhibitory peptide, IκBα, prevents human vascular smooth muscle proliferation. Ann Thorac Surg 1999;67:1227-1231. https://doi.org/10.1016/S0003-4975(99)00252-0
80. Cejkova S, Kubatova H, Thieme F, Janousek L, Fronek J, Poledne R, Kralova Lesna I. The effect of cytokines produced by human adipose tissue on monocyte adhesion to the endothelium. Cell Adh Migr 2019;13:292-301. https://doi.org/10.1080/19336918.2019.1644856
81. Lavie CJ, Milani RV, Ventura HO. Obesity and cardiovascular disease: risk factor, paradox, and impact of weight loss. J Am Coll Cardiol 2009;53:1925-1932. https://doi.org/10.1016/j.jacc.2008.12.068
82. Bakhtiyari M, Kazemian E, Kabir K, Hadaegh F, Aghajanian S, Mardi P, Ghahfarokhi NT, Ghanbari A, Mansournia MA, Azizi F. Contribution of obesity and cardiometabolic risk factors in developing cardiovascular disease: A population-based cohort study. Sci Rep 2022;12:1544. https://doi.org/10.1038/s41598-022-05536-w
83. Cinti S, Mitchell G, Barbatelli G, Murano I, Ceresi E, Faloia E, Wang S, Fortier M, Greenberg AS, Obin MS. Adipocyte death defines macrophage localization and function in adipose tissue of obese mice and humans. J Lipid Res 2005;46:2347-2355. https://doi.org/10.1194/jlr.M500294-JLR200
84. Lumeng CN, Bodzin JL, Saltiel AR. Obesity induces a phenotypic switch in adipose tissue macrophage polarization. J Clin Invest 2007;117:175-184. https://doi.org/10.1172/JCI29881
85. Garaulet M, Hernandez-Morante J, Lujan J, Tebar F, Zamora S. Relationship between fat cell size and number and fatty acid composition in adipose tissue from different fat depots in overweight/obese humans. Int J Obes 2006;30:899-905. https://doi.org/10.1038/sj.ijo.0803219
86. Majka Z, Czamara K, Janus J, Kępczyński M, Kaczor A. Prominent hypertrophy of perivascular adipocytes due to short-term high fat diet. Biochim Biophys Acta Mol Basis Dis 2022;1868:166315. https://doi.org/10.1016/j.bbadis.2021.166315
87. Schusterova I, Leenen F, Jurko A, Sabol F, Takacova J. Epicardial adipose tissue and cardiometabolic risk factors in overweight and obese children and adolescents. Pediatr Obes 2014;9:63-70. https://doi.org/10.1111/j.2047-6310.2012.00134.x
88. Margaritis M, Antonopoulos AS, Digby J, Lee R, Reilly S, Coutinho P, Shirodaria C, Sayeed R, Petrou M, De Silva R. Interactions between vascular wall and perivascular adipose tissue reveal novel roles for adiponectin in the regulation of endothelial nitric oxide synthase function in human vessels. Circulation 2013;127:2209-2221. https://doi.org/10.1161/CIRCULATIONAHA.112.001133
89. Simons PJ, van den Pangaart PS, Aerts JM, Boon L. Pro-inflammatory delipidizing cytokines reduce adiponectin secretion from human adipocytes without affecting adiponectin oligomerization. J Endocrinol 2007;192:289-299. https://doi.org/10.1677/JOE-06-0047
90. Brooks RA. A quantitative theory of the Hounsfield unit and its application to dual energy scanning. J Comput Assist Tomogr 1977;1:487-493. https://doi.org/10.1097/00004728-197710000-00016
91. Tu Y-B, Gu M, Zhou S-Q, Xie G, Liu L-L, Deng F-B, Li K. Pericoronary adipose tissue attenuation in patients with acute aortic dissection based on coronary computed tomography angiography. Quant Imaging Med Surg 2024;14:31. https://doi.org/10.21037/qims-23-253
92. Goeller M, Achenbach S, Cadet S, Kwan AC, Commandeur F, Slomka PJ, Gransar H, Albrecht MH, Tamarappoo BK, Berman DS. Pericoronary adipose tissue computed tomography attenuation and high-risk plaque characteristics in acute coronary syndrome compared with stable coronary artery disease. JAMA cardiol 2018;3:858-863. https://doi.org/10.1001/jamacardio.2018.1997

93. Niccoli G, Scalone G, Crea F. Acute myocardial infarction with no obstructive coronary atherosclerosis: mechanisms and management. Eur Heart J 2015;36:475-481. https://doi.org/10.1093/eurheartj/ehu469
94. Naghavi M, Libby P, Falk E, Casscells SW, Litovsky S, Rumberger J, Badimon JJ, Stefanadis C, Moreno P, Pasterkamp G. From vulnerable plaque to vulnerable patient: a call for new definitions and risk assessment strategies: Part I. Circulation 2003;108:1664-1672. https://doi.org/10.1161/01.CIR.0000087480.94275.97, https://doi.org/10.1161/ 01.CIR.0000087481.55887.C9
95. Klüner LV, Oikonomou EK, Antoniades C. Assessing cardiovascular risk by using the fat attenuation index in coronary CT angiography. Radiol Cardiothorac Imaging 2021;3:e200563. https://doi.org/10.1148/ryct.2021200563
96. Oikonomou EK, Antonopoulos AS, Schottlander D, Marwan M, Mathers C, Tomlins P, Siddique M, Klüner LV, Shirodaria C, Mavrogiannis MC. Standardized measurement of coronary inflammation using cardiovascular computed tomography: integration in clinical care as a prognostic medical device. Cardiovasc Res 2021;117:2677-2690. https://doi.org/10.1093/cvr/cvab286
97. Graby J, Sellek J, Khavandi A, Loughborough W, Hudson B, Shirodaria C, Downie P, Antoniades C, Rodrigues J. Coronary CT angiography derived pericoronary inflammation and bespoke cardiovascular risk prediction in the lipid clinic: beyond the calcium score. Eur Heart J 2022;43:ehac544. 2315. https://doi.org/10.1093/eurheartj/ehac544.2315
98. Dai X, Deng J, Yu M, Lu Z, Shen C, Zhang J. Perivascular fat attenuation index and high-risk plaque features evaluated by coronary CT angiography: relationship with serum inflammatory marker level. Int J Cardiovasc Imaging 2020;36:723-730. https://doi.org/10.1007/s10554-019-01758-8
99. Kato S, Horita N, Hoshino M, Kakuta T, Utsunomiya D. Prognostic Significance of the Perivascular Fat Attenuation Index derived by Coronary Computed Tomography: A Meta-analysis. Hellenic J Cardiol 2022:S1109-9666 (1122) 00097. https://doi.org/10.1016/j.hjc.2022.07.004
100. Antoniades C, Patel P, Antonopoulos AS. Using artificial intelligence to study atherosclerosis, predict risk and guide treatments in clinical practice. Eur Heart J 2023;44:437-439. https://doi.org/10.1093/eurheartj/ehac751