

The role of adipose tissue in cardiovascular health and disease

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Abstract | Accumulating knowledge on the biology and function of the adipose tissue has led to a major shift in our understanding of its role in health and disease. The adipose tissue is now recognized as a crucial regulator of cardiovascular health, through the secretion of several bioactive products, including adipocytokines, microvesicles, and gaseous messengers, with a wide range of endocrine and paracrine effects on the cardiovascular system. The adipose tissue function and secretome are tightly controlled by complex homeostatic mechanisms and local cell–cell interactions, which can become dysregulated in obesity. Systemic or local inflammation and insulin resistance lead to a shift in the adipose tissue secretome from anti-inflammatory and anti-atherogenic towards a pro-inflammatory and pro-atherogenic profile. Moreover, the interplay between the adipose tissue and the cardiovascular system is bidirectional, with vascular-derived and heart-derived signals directly affecting adipose tissue biology. In this Review, we summarize the current knowledge on the biology and regional variability of adipose tissue in humans, deciphering the complex molecular mechanisms controlling the crosstalk between the adipose tissue and the cardiovascular system, and their possible clinical translation. In addition, we highlight the latest developments in adipose tissue imaging for cardiovascular risk stratification, and discuss how therapeutic targeting of the adipose tissue can improve prevention and treatment of cardiovascular disease.

Introduction

Cardiovascular disease (CVD) remains a leading cause of morbidity and mortality despite substantial advances in risk stratification, prevention, and treatment.¹ Obesity, traditionally defined as a BMI ≥ 30

kg/m², is an established cardiovascular risk factor,² predisposing to a range of cardiometabolic abnormalities.³ However, expanding knowledge on the role of the adipose tissue in CVD pathogenesis has revealed a more complex landscape than previously thought. Large-scale epidemiological studies have questioned the exact nature of the association between BMI and adverse outcomes, suggesting an “obesity paradox”, namely the paradoxical survival benefit observed among overweight or even obese individuals compared with their normal-weight counterparts in the general population or in those with chronic diseases.^{4,5} Moreover, the adipose tissue has striking biological variability depending on its location and metabolic state, affecting the individual’s overall cardiometabolic risk.⁶⁻
⁸ Although anthropometric indices such as the waist-to-hip ratio (WHR) were developed to capture variations in adipose tissue distribution,⁹ these parameters only provide information on adipose tissue expansion and do not take into account the dynamic nature of the adipose tissue as an endocrine organ.⁹⁻¹¹ The notion of the adipose tissue as a “biochemical factory” is not a recent one,¹⁰ but the importance of the adipose tissue in cardiovascular health and disease remains the topic of extensive research. As our knowledge on adipose tissue biology continues to expand, the adipose tissue is increasingly being recognised as a crucial regulator of cardiovascular health and disease and as a host of both diagnostic biomarkers and promising therapeutic targets.

In this Review, we present the most recent advances in the past decade in the field of adipose tissue biology and highlight how this knowledge can lead to clinical breakthroughs in cardiovascular diagnostics and therapeutics. First, we review the anatomy, composition, and biology of different adipose tissue depots in both health and disease. We discuss the biological and phenotypic heterogeneity of the adipose tissue and its importance in cardiometabolic health, with a particular emphasis on the role of “dysfunctional” adipose tissue in CVD pathogenesis. We then describe the bidirectional nature of the interactions between the adipose tissue and the cardiovascular system in humans, focusing on the potential role of this crosstalk in obesity-related cardiovascular complications. Next, we review the current state-of-the-art techniques for studying the quality and

quantity of human adipose tissue, and finally highlight the potential of the adipose tissue as a target in future CVD therapeutics.

Adipose tissue in health and disease

Structure, anatomy, and biology

The adipose tissue in the human body can be broadly divided into two main anatomical depots, visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT).^{6,12} VAT in turn can be classified on the basis of its anatomical location as intrathoracic, abdominal, etc., and intrathoracic adipose tissue can be further classified as epicardial adipose tissue (EAT) and pericardial adipose tissue (PAT) on the basis of its location within or outside the human pericardium, respectively¹³. The importance of this classification is highlighted by studies revealing distinct transcriptomic and proteomic profiles between different adipose tissue depots,^{7,14,15} as well as epidemiological studies that reveal a close link between VAT expansion and cardiometabolic risk, as opposed to the neutral or even cardioprotective profile of SAT.⁶ However, regional biological variability has also been described within the same depots. For instance, when compared with gluteal SAT, abdominal SAT has a distinct transcriptomic signature, which resembles that of VAT depots.¹⁶ Substantial variability exists even within the abdominal SAT, with deep SAT (below Scarpa's fascia) exhibiting a metabolic phenotype closer to that of VAT, which is more closely associated with insulin resistance and cardiometabolic risk, compared with superficial SAT.⁸ Similar regional heterogeneity has been described in EAT, with distinct transcriptomic signatures in the peri-ventricular, peri-atrial, and peri-coronary sites.¹⁷

Based on its phenotype, functional role, and gene expression profile, the adipose tissue can be further classified as white or brown. White adipose tissue (WAT) represents most of the adipose tissue mass in humans, whereas brown adipose tissue (BAT) accounts for ~4.3% of the total fat mass in adults and is located in several regions, predominantly in the interscapular and supraclavicular area.¹⁸ An inducible form of BAT, namely beige adipose tissue (also known as brite adipose tissue), can be found interspersed in WAT depots and occurs in response to cold exposure and pharmacological

modulation of WAT.^{19,20} Although BAT or beige adipose tissue activation is traditionally linked to thermoregulatory thermogenesis,¹⁸ this activation might also have an important role in promoting weight loss and insulin sensitivity.²¹

Although adipocytes account for most of the volume of a given adipose tissue depot, being responsible for energy storage in the form of triglycerides, several other cell types exist in the stromal fraction of the adipose tissue.^{7,22} These cell types include inflammatory cells, such as macrophages,²³ lymphocytes,²⁴ and eosinophils,²⁵ fibroblasts, pre-adipocytes, vascular cells that form the adipose tissue microvasculature,⁷ as well as multipotent mesenchymal stem-like cells known as adipose-derived stromal or stem cells.²⁶ Most adipose tissue-resident cells produce and secrete adipocytokines and other mediators that exert autocrine, paracrine, and/or endocrine effects on neighbouring cells or remote tissues and organs.²⁷ Of note, the composition of the adipose tissue secretome is largely depot-specific, and can also be affected by systemic and local factors linked to inflammation, insulin resistance, and obesity.²³ For instance, analysis of adipose tissue-resident cells from different depots has revealed distinct patterns, with visceral adipose-derived stem cells secreting higher levels of pro-inflammatory factors, such as IL-6 and CC motif chemokine 2 (CCL2; also known as MCP1), and lower levels of anti-inflammatory mediators such as adiponectin and IL-10 compared with subcutaneous adipose-derived stem cells.⁷

Research models on adipose tissue biology

Animal models, including rodents, have traditionally been used to study the biological mechanisms of obesity-related cardiometabolic disease.²⁸ However, despite many similarities between the adipose tissue of humans and rodents, there are also substantial disparities. Differences in regulation of lipolysis (for example, α 2-adrenergic receptors and natriuretic peptides regulate lipolysis in humans but not in rodents), the absence of a layer equivalent to human deep SAT or omental adipose tissue, as well as differences in adipose tissue distribution (which preclude the development of translational tools to assess the importance of adipose tissue distribution)²⁸, are important limitations in the

translation of findings from animal studies to humans, highlighting the need for new translational models to investigate the association between adipose tissue and CVD.

Adipose tissue remodelling

Obesity, insulin resistance, diabetes mellitus, and inflammation are all associated with a shift in the phenotype and biology of the adipose tissue.²⁹ The exact nature and degree of these changes are critical in mediating the protective or adverse effects of adipose tissue on CVD pathogenesis. In response to excessive caloric intake, the adipose tissue expands through an increase in adipocyte numbers (hyperplasia) and/or size (hypertrophy).^{30,31} Adipose tissue hyperplasia through mobilization of progenitor cells is traditionally considered as a healthy mechanism of adipose tissue expansion, compared with adipocyte hypertrophy that can lead to dysfunctional, lipid-laden adipocytes, adipose tissue inflammation, oxidative stress, and eventual adipocyte death.³² However, adipose tissue depots differ in their adipogenic capacity. For example, the limited adipogenic capacity of the SAT might promote fat storage in ectopic, visceral depots, predisposing to systemic metabolic complications.³³

In obesity and many chronic diseases (such as diabetes mellitus and atherosclerosis) the adipose tissue is infiltrated by increasing populations of inflammatory cells,^{34,35} such as lymphocytes (including T-helper type 1 (Th1) cells and B cells), neutrophils, macrophages, and mast cells, whereas the population of eosinophils, Th2 cells, and regulatory T cells remains constant or decreases.^{34,36} Macrophages, the predominant inflammatory cells in adipose tissue, exhibit a range of phenotypes, ranging from M1 pro-inflammatory to M2 anti-inflammatory phenotypes.^{37,38} In lean adipose tissue, M2 macrophages predominate as a result of Th2-type cytokines released by Th2 cells and eosinophils. By contrast, in obesity and metabolic disease, adipose tissue infiltration by cells producing Th1-cytokines (such as IFN γ) shifts the macrophage phenotype towards the M1 type.^{29,39} M1 macrophages have also been implicated in the regulation of adipose tissue expansion and ectopic fat deposition through secretion of platelet-derived growth factor- β , which activates pericytes and promotes neoangiogenesis.⁴⁰

Adipose tissue expansion in obesity is also associated with capillary rarefaction, resulting in reduced delivery of nutrients and oxygen to the adipose tissue, and eventually to adipose tissue dysfunction and insulin resistance.⁴¹ Endothelial cell activation, characterised by increased expression of adhesion molecules such as P-selectin and E-selectin that promote inflammatory cell infiltration, and vasomotor dysfunction of the adipose tissue vasculature have also been implicated in the pathogenesis of dysfunctional adipose tissue.⁴² The resulting hypoxia-induced increase in hypoxia-inducible factor 1 α can further promote adipose tissue fibrosis, which is more prevalent in VAT and SAT from obese individuals.⁴³ More recent studies have also implicated lymphatic vessel dysfunction in adipose tissue dysfunction, with evidence showing that leakage of lipid-rich lymph from dysfunctional lymphatic vessels, especially in visceral sites, can stimulate adipogenesis, adipose tissue hypertrophy, and ectopic adipose tissue expansion.⁴⁴

Obesity-related metabolic disease is also associated with changes in the balance between the relatively “protective” BAT and beige adipose tissue phenotype and the “deleterious” WAT phenotype. In mice, both BAT transplantation and WAT “beiging” — a term describing the proliferation in WAT of adipocytes expressing mitochondrial brown fat uncoupling protein 1 (UCP1) — are associated with weight loss and improved insulin resistance.^{21,45} Similarly, in humans, obesity is associated with lower BAT volume,⁴⁶ while decreased expression of UCP1 in human EAT is related to increased adipose tissue oxidative stress and dysfunction.⁴⁷ The effects of BAT on insulin resistance and remote tissues are not only a result of the increased metabolic activity and thermogenic capacity of BAT, but also the release of BAT-specific adipokines (termed “batokines”) which exert beneficial autocrine as well as paracrine and endocrine effects on peripheral tissues, including the cardiovascular system.²⁰ Nevertheless, owing to substantial inter-species differences in the molecular signature and regulation of brown and beige adipocyte formation,¹⁹ our understanding of the role and full therapeutic potential of BAT and beige adipose tissue in humans remains limited.

Finally, further to the changes in adipose tissue composition, obesity, insulin resistance, and diabetes mellitus are also linked to changes in the secretory and biochemical profile of adipose tissue,

consistent with a shift towards a more pro-inflammatory phenotype (Table 1).⁴⁸ For instance, obesity-related insulin resistance is linked to higher circulating levels of retinol-binding protein 4 (RBP4),⁴⁹ visfatin,⁵⁰ chemerin,⁵¹ vaspin,⁵² resistin,⁵³ and to lower levels of omentin 1⁵⁴ and adiponectin.⁵⁵ However, adipokine expression levels in specific adipose tissue depots might not necessarily correlate with the adipokine levels in circulation,⁵⁶ suggesting the existence of complex mechanisms that regulate the biology and secretome of the adipose tissue. As discussed below, this concept of adipokine signalling is central to the adipo-vascular axis,⁵⁷ and provides a mechanistic link between adipose tissue biology and CVD pathogenesis.

BMI as a risk factor: the obesity paradox

On the basis of the results of a large-scale meta-analysis including >30 million individuals, the association between BMI and all-cause mortality in the general population can be described as U-shaped or J-shaped.⁴ The higher risk observed in certain occasions among individuals with low-to-normal BMI values compared with those in the overweight group, especially for short-term (5–10 years) mortality, might be attributed to the effects of chronic diseases (such as cancer and chronic kidney disease) that are associated with a hypercatabolic state.⁵⁸ Inherent limitations of BMI to capture adipose tissue distribution and body composition might also contribute to this paradox, suggesting that the obesity paradox is essentially a “BMI paradox”.⁵⁸ In an analysis of >130,000 UK Biobank participants (aged 60–69 years, without active smoking or disease-associated weight loss, with a follow-up of ≤8.3 years), no significant difference was observed in the risk of death between normal-weight and overweight individuals⁹. However, within each group, higher WHR was significantly associated with an excess mortality, highlighting the limitations of BMI in defining central adiposity.⁹

In some chronic disease states, including patients with heart failure or with metabolic abnormalities, the paradoxical survival benefit of overweight and/or obese individuals compared with their normal-weight counterparts is even more pronounced, with multiple studies showing an inverse association between BMI and adverse events.^{5,59} However, the observed associations are not

necessarily causal in nature. The adipose tissue can respond to inflammatory and cachexia-related signals in chronic disease states, leading to increased lipolysis and volume reduction.^{58,60} In addition, differences in lean body mass (BMI does not differentiate fat from lean body mass) and cardiorespiratory fitness might also have a confounding role, possibly explaining the paradoxical survival benefit observed with increasing BMI levels, particularly among patients with heart failure^{61,62}. Taken together, these paradoxical and apparently contradictory findings reinforce the view that we should look beyond the adipose tissue volume to understand better the mechanisms linking adipose tissue with overall cardiometabolic health.

Adipose tissue and the cardiovascular system

Adipose tissue expansion and dysfunction lead to CVD through a series of interrelated direct and indirect mechanisms. Obesity is known to induce hypertension, possibly through mechanical compression of the kidneys owing to VAT expansion, activation of the sympathetic nervous system activity and the renin-angiotensin-aldosterone system (RAAS) independently of aldosterone, and a mild natriuretic peptide deficiency.^{63,64} Obesity-related adipose tissue inflammation and resulting dysfunction are also crucial components of insulin resistance, which can lead to type 2 diabetes mellitus and its well-known deleterious effects on microvascular and macrovascular function.³⁸ Dysfunctional adipose tissue might also promote thrombosis through increased isoprostane and tissue factor production, as well as by inducing platelet insulin resistance and activation.⁶⁵ In addition to these indirect mechanisms, the adipose tissue exerts direct effects on the cardiovascular system through the secretion of a wide range of bioactive adipocytokines, including adipokines (such as adiponectin) and pro-inflammatory cytokines,⁵⁶ as well as other products, including microRNAs,⁶⁶ microvesicles,⁶⁷ inorganic molecules such as hydrogen sulphide (H₂S),⁶⁸ and fatty acid metabolites.⁶⁹ These molecules can exert autocrine effects on the adipose tissue itself, but can also regulate the biology of adjacent or even distant tissues through endocrine, paracrine,⁷⁰ and vasocrine mechanisms (Figure 1).⁷¹

Effects on the vascular wall

Vascular tone, inflammation, vascular smooth muscle cell (VSMC) migration, endothelial function, and vascular redox state are all under the regulation of adipose tissue-derived products including adipocytokines (Figure 2). While most depots can exert endocrine effects, perivascular adipose tissue (PVAT) is now recognised as a critical regulator of vascular function given its anatomical proximity to the vascular wall, which facilitates a range of direct, paracrine effects.⁷⁰

The adipose tissue regulates the vascular tone in healthy conditions through the release of molecules with vasorelaxant properties, such as adiponectin, which induces 5' adenosine monophosphate-activated protein kinase (AMPK) or RAC- α serine/threonine-protein kinase (AKT)-mediated endothelial nitric oxide synthase (eNOS) phosphorylation,^{56,72} H₂S, which causes activation of ATP-regulated potassium channels,⁶⁸ and palmitic acid methyl ester (PAME), which activates voltage-gated potassium channels.⁶⁹ The decreased production of all these mediators in obesity and insulin resistance might contribute to obesity-related vasomotor dysfunction.^{11,70,73} A 2018 study suggests that PVAT in particular is involved in the circadian regulation of blood pressure through aryl hydrocarbon receptor nuclear translocator-like protein 1 (also known as BMAL1) in brown adipocytes, which regulates local angiotensinogen production⁷⁴ and further contributes to the uptake and metabolism of vasoconstrictors such as noradrenaline.⁷⁵ Furthermore, experimental evidence from mice suggest that reactive oxygen species (ROS), such as NOX4-derived hydrogen peroxide from BAT, can induce cyclic GMP-dependent protein kinase G type- α activation, resulting in reduced vascular contractility.⁷⁶

Adipose tissue-derived molecules further regulate the vascular redox state, and increased vascular oxidative stress has been associated with accelerated biological senescence and adverse clinical outcomes.⁷⁷ NADPH is a potent source of superoxide radicals and signalling ROS in the vascular wall^{48,78,79}. The activity of certain isoforms of NADPH-oxidase (for example, NOX1 and NOX2) is inhibited by antioxidant adipokines such as adiponectin and omentin 1 (by preventing the activation

and membrane translocation of RAC1 and by downregulating p22^{phox} regulatory protein),^{56,73} but promoted by pro-oxidant adipokines such as leptin and resistin, thereby contributing to atherogenesis.⁴⁸ Uncoupling of eNOS through reduced bioavailability of its cofactor tetrahydrobiopterin (BH₄) is another crucial mechanism contributing to deleterious superoxide production.⁸⁰ While adiponectin and other adipokines such as C1q/tumor necrosis factor-related protein 9 (CTRP) promote eNOS phosphorylation through activation of the AMPK pathway and improved eNOS coupling,^{56,81,82} chemerin has opposing effects, promoting eNOS uncoupling and decreasing nitric oxide (NO) production in favour of superoxide.⁸³ Vascular inflammation is further promoted by expression of endothelial cell adhesion molecules, which is induced by adipokines such as visfatin,⁸⁴ and adipose tissue-derived pro-inflammatory cytokines such as IL-1 β and tumour necrosis factor (TNF).⁴⁸ Some adipokines, such as leptin, have multiple, and often contradicting effects on different cell types and in different disease substrates.⁸⁵ For example, whereas endothelial leptin signalling is considered to be protective against neointima formation, obesity-induced leptin resistance can reverse this balance towards an atherogenic phenotype.⁸⁶ Central signalling pathways, such as the nuclear factor (NF)- κ B pathway, have a critical role in orchestrating this range of pro-atherogenic effects and are either inhibited (for example, by adiponectin, and fibroblast growth factor 21) or activated (for example, by leptin, visfatin, and RBP4) by specific adipokines.^{48,57,84}

MicroRNAs — small RNAs involved in post-transcriptional regulation — are also produced by the adipose tissue, and their profile changes in response to obesity, insulin resistance,⁸⁷ and coronary artery disease (CAD).⁸⁸ MicroRNAs have been shown to orchestrate several processes, ranging from the recruitment of inflammatory cells to the dysfunctional adipose tissue,⁸⁹ to the regulation of insulin sensitivity.⁹⁰ However, adipose tissue-derived microRNAs packed in extracellular vesicles such as exosomes and microparticles are also released into the circulation, enabling the adipose tissue to regulate gene expression in remote tissues.⁶⁶ The spectrum of microRNAs is vast, and numerous microRNAs have been linked to adipose tissue browning,⁹¹ inflammation,⁸⁷ myocardial fibrosis, atherosclerosis, and VSMC activation.^{66,91,92} Furthermore, VAT-derived exosomes from mice with high

fat diet-induced obesity have been shown to promote M1 pro-inflammatory polarization of macrophages and to accelerate atherosclerosis in *Apoe*^{-/-} mice, whereas no such effects were described for SAT-derived or VAT-derived exosomes from wild-type mice,⁶⁷ suggesting depot-specific variations in exosome production. The differential regulation of adipose tissue-derived exosomes and microRNAs in obesity and diabetes mellitus, as well as the proven effects of weight loss and exercise on the levels of specific microRNAs in the adipose tissue, have highlighted microRNAs as potential therapeutic targets in obesity-related CVD.⁹³

Gaseous messengers represent another class of mediators of the adipose tissue–cardiovascular system interactions. Gaseous messengers include NO, which is produced by adipocyte or macrophage NOS and exerts paracrine anti-inflammatory effects, and adipose tissue-derived H₂S. Disturbed production of these mediators in obesity has been associated with endothelial dysfunction and with pro-atherogenic effects.^{68,94,95}

Local immunological properties of PVAT are increasingly being recognised as critical regulators of PVAT function. Further to the role of macrophage polarization in regulating PVAT function,³⁸ experimental evidence suggests that PVAT eosinophils regulate the anticontractile response of PVAT,²⁵ whereas PVAT-residing B1 cells exert atheroprotective effects through the production of IgM against oxidation-specific epitopes on LDL.²⁴ PVAT inflammation is also associated with vascular dysfunction in hypertension, and is mediated by a range of cytokines and chemokines such as CC-chemokine ligand 5 (CCL5; also known as RANTES) that mediate T-cell infiltration in the perivascular space,⁹⁶ as well as with complement C5a-mediated decrease in adiponectin production, which promotes hypertensive vascular inflammation.⁹⁷

The importance of sensory innervation of the adipose tissue has also been described. Sensory nerves within PVAT contribute to neurogenic vasorelaxation and crosstalk with adipocytes, leading to leptin-induced relaxation mediated by calcitonin gene-related peptide, a mechanism that is downregulated with reduced oxygenation, such as in obesity-induced adipose tissue dysfunction.⁹⁸

Effects on the heart and cardiomyocytes

The effects of the adipose tissue on the cardiovascular system are not limited to the vascular wall, but important interactions have also been reported with the myocardium (Figure 3).⁹⁹ Of all the adipose tissue depots, EAT is most closely associated with myocardial biology, given the absence of an anatomical barrier between the EAT and the myocardium and the vascularization of EAT by the coronary vessels, which allow a paracrine and vasocrine crosstalk between the two organs. EAT provides mechanical, thermogenic, and possibly metabolic support (in the form of free fatty acids) to the adjacent myocardium.¹³ The EAT is further characterised by a distinctive transcriptomic signature, enriched in genes involved in inflammation, thrombosis, and extracellular matrix remodelling.¹⁷ The close interaction between the EAT and its neighbouring structures might explain further site-specific variations in its transcriptome. For instance, compared with non-pericoronary EAT, pericoronary EAT expresses high levels of BAT-related genes such as UCP1, whereas peritrial EAT is characterised by overexpression of genes involved in cardiac muscle contraction.¹⁷

Our group has shown that adipose tissue-derived adiponectin exerts anti-oxidant effects on cardiomyocytes through suppression of myocardial NADPH-oxidase activity, by preventing AMPK-mediated membrane translocation of RACc1 and p47^{phox}.¹⁰⁰ This action might represent a protective mechanism to prevent deleterious arrhythmogenesis and other effects of myocardial oxidative stress.¹⁰¹ Other protective effects include the autocrine and paracrine effects of WNT1-inducible-signalling pathway protein 2 on promoting insulin sensitivity and heart hyperplasia.¹⁰² Conversely, RBP4 reduces the expression of the insulin-dependent glucose transporter 4 (GLUT4) in cardiomyocytes, thereby promoting insulin resistance, and also induces cardiomyocyte hypertrophy by activating Toll-like receptor 4-dependent inflammatory pathways, suggesting a vicious circle between insulin resistance and heart failure.¹⁰³ Cardiomyocyte metabolism is also affected by activin A, which impairs insulin action via upregulation of miR-143,¹⁰⁴ whereas chemerin induces cardiomyocyte apoptosis through reduced AKT phosphorylation and increased cleavage of caspase 9.¹⁰⁵ Studies in rat cardiomyocytes incubated with conditioned media from EAT isolated from patients

with diabetes mellitus have shown that products secreted by the EAT impair cardiomyocyte contractile function and mitochondrial β -oxidation via activation of the cardiac-specific RAAS system and induction of miR-208a.¹⁰⁶ Certain adipokines, such as osteopontin and leptin (known as “adipofibrokinases”) also promote cardiac fibrosis, possibly through modulation of fibroblast senescence¹⁰⁷ or through mineralocorticoid receptor-dependent and oxidative stress-dependent pathways, which regulate the production of end effectors (such as transforming growth factor- β ; TGF- β) responsible for the synthesis of extracellular matrix in cardiac fibroblasts.¹⁰⁸ EAT might also contribute to atrial fibrillation pathogenesis through the release of activin A, which promotes atrial fibrosis and remodelling.^{109,110} In addition, increased EAT aromatase activity might be involved in arrhythmogenesis through local steroid conversion and increased 17 β -estradiol levels.¹¹¹

Overall, phenotypic, proteomic, and structural changes in EAT are evident in several cardiac conditions, including atrial fibrillation, which is associated with fibrotic changes in subepicardial adipose tissue.¹¹² Heart failure and cardiomyopathy are also associated with extensive remodelling of the EAT extracellular matrix,¹¹³ upregulation of EAT lipolysis leading to local release of potentially harmful lipolytic intermediates,¹¹⁴ and loss of BAT features, which are believed to exert protective effects against the development of heart failure.¹¹⁵

Bidirectional crosstalk

Changes in cardiovascular biology can affect adipose tissue biology in a bidirectional loop, with important implications in CVD pathogenesis and, as discussed below, diagnosis. Early studies demonstrated the upregulation of pro-inflammatory adipocytokines and downregulation of adiponectin in PVAT following vascular injury in mice, effects that were mediated by upregulation of TNF¹¹⁶. Our group later demonstrated that in the presence of increased vascular oxidative stress, the release of lipid peroxidation products (such as 4-hydroxynonenal) into the surrounding PVAT activates peroxisome proliferator-activated receptor- γ (PPAR γ) signalling, leading to increased adiponectin biosynthesis, which then exerts antioxidant effects on the vascular wall in a protective, feedback

mechanism.^{56,73,117} Our group also described that in the presence of coronary inflammation and atherosclerotic disease, the release of pro-inflammatory mediators from the vascular wall into the surrounding PVAT results in impaired adipocyte differentiation and intracellular lipid formation, with important implications in cardiovascular diagnostics.¹¹⁸ This interplay can be mediated by various molecules, including endothelium-derived microparticles containing miR-19b, which have been shown to induce PVAT inflammation and promote atherogenesis in *ApoE*^{-/-} mice.¹¹⁹

Such paracrine interactions are not confined to the vascular wall. Our group has uncovered similar links between the myocardium and EAT. Similarly to the vessels, myocardial-derived oxidation products lead to PPAR γ -mediated upregulation of adiponectin biosynthesis in the adjacent EAT, which then exerts antioxidant effects on the cardiomyocytes.¹⁰⁰ In addition to the EAT, we have also identified communication links between the myocardium and remote adipose tissue depots, establishing that among patients with advanced atherosclerosis, circulating brain natriuretic peptide (BNP) levels, rather than systemic inflammation, are the principal driver of circulating adiponectin levels.²³ The existence of inside-to-outside signalling pathways is further supported by data from other studies. In mice, natriuretic peptides stimulate adipose tissue browning,¹¹⁹ improving energy expenditure and insulin sensitivity.¹²⁰ By contrast, atrial myocyte-secreted atrial natriuretic peptide (ANP) is a major adipogenic factor mediated by natriuretic peptide receptor A (NPRA) pathway activation, contributing to a potentially pro-arrhythmogenic crosstalk between EAT expansion and mechanical function of the atrial myocardium.¹²¹ Finally, similar to coronary inflammation,¹¹⁸ in myocardial disease states such as systolic heart failure, the local release of inflammatory mediators (such as IL-6 and TNF) can trigger EAT lipolysis, thus providing a possible mechanistic explanation for the observed negative association between EAT volume and left ventricular ejection fraction in these patients.⁶⁰

Effects of ectopic fat deposition

Further to the traditional adipose tissue depots, ectopic fat deposition either in the liver (non-alcoholic fatty liver disease; NAFLD), the myocardium, or in skeletal muscle is increasingly recognised as a cardiometabolic risk factor, and has been linked to increased prevalence of coronary atherosclerosis and higher incidence of adverse cardiovascular events.^{122,123} Indeed, clinical studies have established hepatic and cardiac steatosis as hallmarks of type 2 diabetes mellitus, independently of BMI, and have further linked ectopic fat expansion in these depots to marked abnormalities in cardiac structure and energetics.¹²⁴ Intrahepatic triglyceride content (IHTG) has been proposed as a better marker of insulin resistance and dysregulated fatty acid transport than VAT.¹²⁵ Indeed, VAT volume and the presence of insulin resistance are not associated in individuals matched for IHTG, suggesting that the close association between visceral obesity and metabolic disease is mediated by a link between VAT expansion and IHTG.¹²⁵ Although the exact pathophysiological mechanisms linking IHTG and NAFLD with CVD are unclear, an imbalanced adipokine profile in obesity and metabolic disease (characterised by decreased adiponectin levels and increased leptin, visfatin, chemerin, and resistin levels) seems to contribute to metabolic inflammation, driving ectopic intrahepatic fat accumulation.¹²⁶ Intrahepatic fat is in turn associated with hepatic and/or peripheral insulin resistance, dyslipidaemia, and secretion of several pro-inflammatory and pro-atherogenic factors, and is further linked to early alterations in cardiac substrate metabolism, as well as functional, structural, and proarrhythmic cardiac changes,¹²³ even though the causality of the observed associations is not yet established. In addition to intrahepatic fat, a community-based study of 3,051 participants identified intramuscular adipose tissue expansion as an independent risk factor for the presence of coronary atherosclerosis, further highlighting the importance of ectopic fat deposition in CVD.¹²⁷

Effects on cardiovascular outcomes

The association between the adipose tissue and CVD is supported by numerous clinical studies. Results from a large-scale, Mendelian randomization analysis revealed a positive, causal association between higher levels of both general and central adiposity with CAD, stroke, and type 2 diabetes mellitus, as

well as associations with left ventricular hypertrophy, circulating IL-6 levels, and dyslipidaemia.¹²⁸ A series of studies, including evidence from the landmark Dallas and Framingham Heart Studies, have demonstrated a positive association between visceral adiposity, but not total or subcutaneous adiposity, with incident hypertension,¹²⁹ as well as an incremental value for VAT beyond BMI for the prediction of incident CVD.^{6,130} Conversely, EAT volume is independently and positively associated with coronary stenosis, myocardial ischaemia, major adverse cardiac events,¹³¹ incidence of atrial fibrillation,¹³² and even clinical presentation and outcomes in patients with pericarditis.¹³³ Beyond volumetric fat assessment, adipose tissue quality and, more specifically, supraclavicular BAT activity have been shown to be inversely associated with arterial inflammation and the risk of future cardiovascular events in humans.¹³⁴ Other studies have explored the clinical importance of the circulating adipokine profile. Two meta-analyses of prospective studies have revealed a positive association between circulating adiponectin levels with coronary heart disease recurrence and with all-cause and cardiovascular mortality among patients with established CVD.⁵⁵ Other studies have linked high resistin levels to increased risk of all-cause and cardiovascular death,⁵³ high visfatin levels to increased risk of adverse cardiac events among patients with myocardial infarction,¹³⁵ and high RBP4 levels to a higher incidence of CVD.⁴⁹

Noninvasive phenotyping of adipose tissue

Adipose tissue phenotyping for cardiometabolic risk stratification in the clinical setting can be performed in an inexpensive way through simple anthropometric measurements. For instance, in addition to the calculation of BMI, simultaneous interpretation of waist circumference and fasting plasma triglyceride concentration (a combination referred to as “hypertriglyceridaemic waist”) has shown good diagnostic accuracy for the identification of men with the so-called atherogenic metabolic triad (elevated insulin, apolipoprotein B, and small-dense LDL levels in plasma), who are at high risk of CAD.¹³⁶ However, the inherent limitations of traditional anthropometric indices in explaining the association between obesity and CVD have led to the development of several imaging modalities that

can extract both quantitative and qualitative features of adipose tissue distribution and composition (Figure 4). Each imaging technique has different strengths and limitations, as summarized in Table 2.

Dual energy X-ray absorptiometry (DEXA). DEXA is a modality commonly used to measure body fat mass, and relies on the analysis of the body absorption of two X-ray beams at different energy levels. Despite being a fairly easy, widely available modality, DEXA cannot easily characterize distinct adipose tissue depots and can have practical limitations when imaging morbidly obese individuals.¹³⁷

Ultrasound and transthoracic echocardiography. Ultrasound can be used to assess subcutaneous (deep versus superficial SAT) and gluteal adipose tissue thickness⁸. Transthoracic echocardiography can provide an easy,¹³⁸ although operator-dependent, assessment of EAT thickness.

CT imaging and MRI. Use of CT imaging enables to quantify accurately adipose tissue volumetric characteristics in different depots by applying standardized CT attenuation thresholds and segmentation algorithms, at the cost of radiation exposure.⁶ By contrast, use of MRI avoids radiation exposure at the cost of longer acquisition times and reduced spatial resolution.¹³⁹ In addition, when combined with nuclear MR spectroscopy, MRI can allow noninvasive detection of adipose tissue browning.¹⁴⁰

[PET–CT and PET–MRI. Qualitative information on adipose tissue composition can be extracted by using ¹⁸Fluorodeoxyglucose (FDG) PET–CT or PET–MRI, where FDG uptake reflects the metabolic and inflammatory activity of adipose tissue.^{141–143} High ¹⁸F-FDG uptake by coronary PVAT has been linked to drug-eluting stent-induced coronary hyperconstricting responses in pigs in vivo,¹⁴² and with vasospastic angina¹⁴³ and the extent of coronary atherosclerosis¹⁴¹ in humans.

[Fat Attenuation Index. In a study published in 2017, our group showed that routine CT imaging can provide sufficient information to identify the composition and biology of the adipose tissue by means of the standardized attenuation of the CT signal for the adipose tissue (adipose tissue CT attenuation).¹¹⁸ To this end, we developed a novel CT-derived metric of adipose tissue attenuation (followed by appropriate post-processing adjustments), namely the Fat Attenuation Index (FAI), that reflects the degree of adipocyte differentiation and lipid accumulation in a given adipose tissue

depot.¹¹⁸ The FAI of remote depots such as VAT and SAT is inversely associated with insulin resistance, independently of adipose tissue volume, possibly owing to the negative association of the FAI with adipocyte size and hypertrophy, which are linked to adipose tissue dysfunction and metabolic disease.^{118,144} However, we did not find an association between perivascular FAI (FAI_{PVAT}) and insulin resistance, suggesting that FAI_{PVAT} is independent of systemic factors¹¹⁸ and is mediated by local, paracrine interactions.^{56,73} Indeed, we had previously observed that the release of pro-inflammatory mediators from the diseased coronary vessel blocks adipocyte differentiation in the adjacent PVAT, creating a gradient of increasing adipocyte size and lipid accumulation from the PVAT adjacent to the diseased vascular wall to PVAT in distal regions. By developing a new technology that allowed a 3D analysis of FAI changes around the coronary vessels on coronary CT angiograms, we demonstrated that FAI_{PVAT} was strongly associated with the presence of CAD, could reliably separate unstable from stable lesions in patients with acute coronary syndromes, and exhibited dynamic changes in response to fluctuations in coronary inflammation, suggesting a novel, noninvasive, adipose tissue-based biomarker of vascular inflammation.¹¹⁸

Other techniques. New experimental imaging techniques provide an insight into adipose tissue structural changes, including browning. Diffuse optical spectroscopy techniques can detect changes in SAT structure following weight loss in humans, correlating with changes in adipocyte size, haemoglobin levels, and water content,¹⁴⁵ and can also reliably assess adipose tissue browning and the transitioning to a beige phenotype in adipose tissue explants.¹⁴⁶ In vivo xenon-enhanced CT has been shown to detect BAT through accumulation of the lipophilic gas xenon in BAT following stimulation of thermogenesis.¹⁴⁷ Finally, advanced videomicroscopy techniques can now assess the vasomotor function of small VAT arterioles in obese individuals, and can be used to evaluate the response of pharmacological interventions targeting the adipose tissue.¹⁴⁸

Targeting the adipose tissue in CVD

Several experimental therapeutic approaches targeting the adipose tissue have shown cardiovascular benefit in animal models or early preclinical studies. In most cases, the clinical translation of adipose tissue-targeting approaches into safe, inexpensive, and effective interventions remains a lengthy and often unsuccessful process. Nevertheless, simple lifestyle interventions and commonly used medications can improve adipose tissue function with a substantial cardiovascular benefit.

Antihyperglycaemic medications

Ever since the ORIGIN trial¹⁴⁹ showed that providing basal insulin to normalize fasting plasma glucose levels did not reduce cardiovascular events in patients with cardiovascular risk factors plus dysglycaemia, several trials on different classes of antihyperglycaemic medications, including glucagon-like peptide (GLP1) agonists (such as liraglutide),¹⁵⁰ dipeptidyl peptidase 4 (DPP4) inhibitors (sitagliptin)¹⁵¹, and sodium-glucose transporter 2 (SGLT2) inhibitors (such as empagliflozin)¹⁵², have demonstrated significant cardiovascular benefits among patients with diabetes. Therefore, it has been hypothesized that the cardioprotective effects of these interventions are independent of their antihyperglycaemic effects.

GLP1 agonists and DPP4 inhibitors (gliptins). GLP1 is an incretin that is mainly produced by the intestinal epithelial endocrine L-cells in response to meal intake, and is responsible for insulin secretion, glucagon inhibition, and decreased gastrointestinal motility in the post-prandial setting.¹⁵³ GLP1 is inactivated by DPP4, an enzyme that was found to be expressed in the adipose tissue.^{154,155} As such, GLP1 agonists and DPP4 inhibitors are now increasingly being used in the management of type 2 diabetes mellitus, and have been shown to improve cardiovascular outcomes in clinical trials.^{150,151} Evidence suggest that the adipose tissue might have an important role in these observed effects. DPP4 is an adipokine that exerts autocrine and paracrine effects on the adipose tissue and correlates with adipocyte size and several metabolic syndrome parameters¹⁵⁴. Studies in animal models have shown that DPP4 inhibition prevents obesity-associated inflammation and insulin resistance by regulating

M1/M2 macrophage polarization in VAT,¹⁵⁵ and blocks adipose tissue fibrosis possibly through neuropeptide Y activation.¹⁵⁶ In patients with type 2 diabetes, treatment with DPP4 antagonists has been shown to reduce hepatic fat content, and in women, possibly also reduces myocardial fat content¹⁵⁹. Direct GLP1 agonism in cultured adipocytes induces adiponectin expression through the protein kinase A pathway, while inhibiting the expression of pro-inflammatory adipokines¹⁵⁷, and has been shown to promote WAT browning in mice through a sirtuin 1-dependent mechanism¹⁵⁸. In patients with type 2 diabetes, treatment with the GLP1 agonist liraglutide causes a rapid, significant reduction in EAT volume¹⁵³.

SGLT2 inhibitors (gliflozins). SGLT2 is a sodium-glucose transporter responsible for renal glucose reabsorption. While pharmacological SGLT2 inhibition is targeted at decreasing blood glucose levels, SGLT2 inhibition has also been shown to exert direct adipose tissue effects.¹⁵² These effects include reduced expression of pro-inflammatory chemokines, increased insulin sensitivity, and adipocyte differentiation in EAT explants,¹⁶⁰ as well as a marked reduction in the amount of EAT in humans,¹⁶¹ which might explain the cardioprotective profile of SGLT2 inhibitors described in clinical trials.¹⁵² This cardioprotective effect might be mediated by a negative caloric balance caused by the loss of glucose in urine, as well as by the higher levels of visceral adiposity found in individuals with type 2 diabetes compared with individuals with normoglycaemia, independently from total adiposity levels.¹⁶²

PPAR γ agonists. The clinical benefit and safety profile of targeting the PPAR γ axis remains contentious, ever since a meta-analysis showed an increased risk of CVD in patients treated with rosiglitazone (a member of the thiazolidinediones group).¹⁶³ Treatment with pioglitazone in animal models has been shown to promote atherosclerotic plaque stability, affecting the outside-to-inside effects of PVAT through downregulation of PVAT inflammation and inflammatory adipokine expression profile,¹⁶⁴. Saroglitazar, another PPAR γ agonist, prevents obesity-induced adipose tissue dysfunction in mice by limiting diet-induced adipocyte hypertrophy, cell damage, and extracellular matrix deposition.¹⁶⁵ As

PPAR γ is a critical regulator of adipogenesis, PPAR- γ agonists might also exert beneficial effects by promoting adipocyte differentiation, predominantly in the subcutaneous depot,¹⁶⁶ thus creating a “metabolic sink” and protecting against VAT expansion and ectopic fat deposition.

Other cardiovascular medications

The adipose tissue is a target of several other commonly used medications. The adipose tissue produces both angiotensinogen and angiotensin II, therefore contributing to local and possibly systemic activation of the RAAS.¹⁶⁷ The adipocytes also express both type 1 and type 2 angiotensin II receptors, which are involved in autocrine, paracrine, and endocrine signalling.¹⁶⁷ Activation of the type 1 angiotensin II receptor in *ApoE*^{-/-} mice promotes M1 macrophage polarization and osteopontin expression in PVAT and increases gelatinolytic activity in the aorta, contributing to aortic aneurysm formation¹⁶⁸. Type 2 angiotensin II receptor activation in cultures of mouse primary white adipocytes promotes adipose browning and BAT adipogenesis through PPAR γ activation.¹⁶⁷ Mineralocorticoid-receptor activation is involved in adipocyte development, but increased activation in disease states promotes oxidative stress, inflammatory adipokine expression, and dysregulates adipocyte autophagy.¹⁶⁹ Therefore, pharmacological modification of the RAAS in the adipose tissue might mediate part of the beneficial effects of angiotensin-converting enzyme inhibitors, angiotensin II-receptor blockers, aldosterone-receptor antagonists (such as spironolactone), or novel therapeutic agents¹⁷⁰.

Other medications might act in a synergistic way with BAT activation to promote the beneficial effects of the medication. For example, atorvastatin accelerates the hepatic uptake of lipoprotein remnants generated by BAT activation, further promoting the lipid-lowering and anti-atherogenic effects of atorvastatin.¹⁷¹ Methotrexate decreases the expression of pro-inflammatory cytokines in PVAT and promotes adiponectin expression, possibly through increased AMPK phosphorylation, therefore restoring eNOS phosphorylation and endothelial function.¹²⁸ Given the demonstrated cardiovascular benefits of anti-inflammatory biological agents such as canakinumab in patients with

established CVD,¹⁷² pharmacological modulation of adipose tissue inflammation should be further explored in the future.

Exercise and diet

The effects of obesity on cardiovascular parameters, such as the association with concentric left ventricular remodelling, are reversible with weight loss.¹⁷³ Caloric restriction improves vascular insulin sensitivity and attenuates the age-related increase in pro-inflammatory cytokine production in PVAT in rats,¹⁷⁴ whereas isocaloric intermittent fasting in mice prevents obesity-related metabolic dysfunction through increased adipose tissue thermogenesis and fasting-mediated periodic upregulation of VEGF in WAT, which is linked with M2 macrophage polarization and WAT browning.¹⁷⁵ Aerobic exercise in male rats decreases the levels of circulating insulin, leptin, and TNF, reduces the expression of the inducible isoform of NOS in PVAT, and restores the anticontractile vascular effect of PVAT compared with sedentary rats.¹⁷⁶ Of note, clinical studies in adult men suggest that exercise-induced weight loss is more effective in improving circulating adipokine profiles and insulin resistance than dieting alone.¹⁷⁷ The beneficial effects of exercise without caloric restriction on fat reduction, insulin resistance,¹⁷⁸ and improvement in circulating adipokine profile,¹⁷⁷ have long been documented in randomized, controlled, clinical trials.¹⁷⁸ High-intensity, interval training has been shown to be particularly effective in reducing total adipose tissue and VAT mass in adults and in increasing cardiorespiratory fitness in obese children^{179,180}; nevertheless, meaningful weight loss can also be achieved by simple activities such as active commuting.¹⁸¹

Bariatric surgery

Bariatric surgery, most commonly Roux-en-Y gastric bypass (RYGB), is usually reserved as a last resort to treat morbid obesity and obesity-related metabolic complications, and has been found to be superior to intensive medical therapy in resolving hyperglycaemia among patients with type 2 diabetes mellitus,¹⁸² with long-lasting benefits for weight loss and prevention of metabolic disease.¹⁸³

The beneficial effects of bariatric surgery can be attributed both to weight reduction per se, as well as to increased production of postprandial GLP1 and GLP1-stimulated insulin secretion.¹⁸⁴ A range of beneficial changes, including reduced macrophage and T cell infiltration into the adipose tissue,¹⁸⁵ increased circulating and adipose tissue-secreted adiponectin levels, as well as decreased lipolysis and adipocyte cell size, might also account for the beneficial effects of bariatric surgery.¹⁸⁶

Experimental interventions

BAT activation and adipose tissue browning. Less than one half of BAT volume in humans is stimulated by cold exposure, while men with obesity have significantly lower BAT activation than men with normal weight, suggesting a promising therapeutic potential for adipose tissue browning in humans.¹⁸ Whereas in rodents, WAT browning has been reported in response to exercise¹⁸⁷ or intermitted fasting,⁴⁵ in humans, exercise alone or caloric restriction-induced weight loss do not promote BAT activation or WAT browning.¹⁸⁸⁻¹⁹⁰ Pharmacological modulation of BAT activity and WAT browning in animal models can be achieved by targeting VEGF receptor 1¹⁹¹ and by administration of retinoic acid¹⁹² or tetrahydrobiopterin,¹⁹³ whereas in humans, thyroid hormone stimulation¹⁹⁴ and β 3-adrenergic agonists have been reported to stimulate BAT activity.¹⁹⁵ Of note, nanoparticles targeted to the adipose tissue might improve the selectivity and therefore safety of therapeutic interventions, such as delivery of microRNAs.¹⁹⁶

Adipose-derived stem cells. Adipose-derived stem cells have emerged as crucial targets in CVD given their cardioprotective and regenerative potential. For instance, exosomes from adipose-derived stem cells have been shown to protect cardiomyocytes against ischaemia–reperfusion injury.¹⁹⁷ Advances in stem cell engineering have also enabled the use of adipose-derived stem cells for myocardial tissue repair, with promising findings from animal studies. Compared with saline, infusion of adipose-derived stem cells into the left ventricle in rat models of coronary artery ligation resulted in significantly improved left ventricular systolic function at 12 weeks.¹⁹⁸ Moreover, in a porcine model of myocardial

infarction intracoronary infusion of autologous adipose-derived stem cells promoted cardioprotective and reparative mechanisms and improved myocardial perfusion, despite showing no effects on the systolic or diastolic ventricular function.¹⁹⁹

Conclusions

The adipose tissue is a dynamic organ, involved in a range of pleiotropic interactions with the cardiovascular system. As such, the adipose tissue is increasingly being recognised both as a crucial regulator of cardiovascular health and as a driver of CVD pathogenesis. In the modern era of precision medicine, our expanding knowledge on adipose tissue biology might enable us to overcome the limitations of the traditional anthropometric indices of obesity and to move closer to an individualised understanding of the adipose tissue and its contribution to cardiometabolic health. Novel, noninvasive techniques of adipose tissue phenotyping have the potential to transform cardiovascular risk stratification, whereas established and experimental pharmacological and other interventions can modify an individual's adipose tissue profile with beneficial effects in both primary and secondary CVD prevention. Importantly, a substantial body of evidence suggests that simple lifestyle interventions, including exercise and diet, are effective in promoting a healthy adipose tissue phenotype and even in reversing adipose tissue dysfunction and related adverse cardiometabolic effects. The adipose tissue, long believed to be a foe of the cardiovascular system, could therefore be turned into a powerful ally in our fight against CVD, by providing a range of prognostic biomarkers and therapeutic targets.

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E. K. O. performed the literature review and prepared the figures and tables and wrote the manuscript before submission. C. A. provided scientific direction, and wrote and reviewed the manuscript before submission.

Competing interests

The methods for analysis of perivascular Fat Attenuation Index described in this manuscript are subject to patent applications, numbers PCT/GB2015/052359 and PCT/GB2017/053262. C.A. is a founder and shareholder of Caristo Diagnostics, a CT-image analysis company. C.A. has received research funding from Sanofi and Novo Nordisk, and a consultancy fee from Mitsubishi-Tanabe.

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Key points

- The adipose tissue is a crucial regulator of cardiovascular health and exerts both protective and deleterious effects on the cardiovascular system.

- The biological profile of the adipose tissue largely depends on its expansion, body distribution, quality, and differences in local biology.
- The adipose tissue can affect local cardiovascular biology through the secretion of adipocytokines with endocrine and/or paracrine effects.
- Conversely, pro-inflammatory and oxidative stimuli in diseased vessels and/or myocardium can modify adipose tissue biology, suggesting a bidirectional interplay between the adipose tissue and the cardiovascular system.
- Several traditional and experimental imaging modalities can be exploited to characterise both quantitative and qualitative adipose tissue features with important implications in cardiometabolic risk stratification.
- The adipose tissue represents a promising therapeutic target in cardiovascular therapeutics and might mediate the cardiovascular benefit observed with different pharmacological, lifestyle, and other interventions.

Figure 1. Effects of the adipose tissue in the cardiovascular system. The adipose tissue exerts direct effects on the cardiovascular system through the secretion of a wide range of bioactive products, including adipocytokines, microvesicles, inorganic molecules, and reactive oxygen species. **a** | Adipose tissue products from remote depots, such as the subcutaneous adipose tissue (SAT), are released into the bloodstream through the adipose tissue microvessels and can reach distant sites (such as the heart and arteries) where they exert their biological effects in an endocrine manner. **b** | In addition to these endocrine effects, perivascular adipose tissue (PVAT) and epicardial adipose tissue (EAT) can exert direct effects on the adjacent vascular wall or myocardium, respectively, through the paracrine release of bioactive mediators. Given that PVAT is often contiguous to the outer adventitial layer of the vascular wall, the vasa vasorum might mediate the local transport of these molecules. **c** | In some cases, PVAT-released products can reach the lumen of the adjacent vessel and travel downstream, thereby regulating the biology of entire vascular beds in a vasocrine manner.

Figure 2. Interplay between the adipose tissue and the vascular wall. The adipose tissue AT is involved in a bidirectional interplay with the vascular wall, mediated by the release of several products with endocrine (by release into the systemic bloodstream) and/or paracrine (local) effects. Among all

adipose tissue depots, the perivascular adipose tissue (PVAT) is now recognized as crucial regulator of vascular biology, given its anatomical proximity to the vessels that facilitates paracrine interactions. **a** | The adipose tissue releases a range of bioactive products, including adipokines (such as adiponectin, leptin, and resistin), chemokines, cytokines, gaseous messengers such as hydrogen sulphide (H₂S) and nitric oxide (NO), fatty acids such as palmitic acid methyl ester (PAME), reactive oxygen species, and microparticles that can carry microRNAs and other molecules to the adjacent vessel. **b** | Inside the vascular wall, these molecules have pleiotropic effects on multiple targets and have been involved in the regulation of local redox state (through modulation of NADPH-oxidase activity and endothelial NO synthase (eNOS) coupling), endothelial function (through regulation of eNOS activity and NO bioavailability), local endothelial cell activation, inflammation (such as the regulation of M1/M2 macrophage polarization), vascular smooth muscle cell (VSMC) migration, neointima formation, and vascular tone. **c** | In addition to these outside-to-inside signals, vascular inflammation and oxidative stress can also affect the adipose tissue (particularly PVAT) biology in an inside-to-outside manner. Inflammatory signals (such as pro-inflammatory cytokines) or lipid peroxidation products (such as 4-hydroxynonenal) can diffuse to the adjacent PVAT and activate signalling pathways in adipocytes. RAAS, renin–angiotensin–aldosterone system.

Figure 3. Interplay between the adipose tissue and the myocardium. A continuous crosstalk exists between the myocardium and the adipose tissue. Remote adipose tissue depots can modify cardiac biology through the release of bioactive products into the bloodstream (endocrine signalling). The epicardial adipose tissue (EAT), the adipose tissue layer that lies on the surface of the human heart inside the visceral pericardium, also interacts with adjacent cardiomyocytes and extracellular matrix in a paracrine manner. The EAT effects on cardiac biology largely depend on the nature of its secretome, which is characterised by a wide range of products, including adipocytokines, microparticles, gaseous messengers, and lipids. Systemic factors, such as obesity, systemic inflammation, and insulin resistance, are important modifiers of the adipose tissue secretome and can shift the balance towards the secretion of products with deleterious cardiac effects. Adipose tissue-derived molecules are involved in several biological processes in the myocardium, such as hypertrophy, redox balance, contractility, inflammation, and fibrosis, and in clinical conditions such as arrhythmogenesis and heart failure. The EAT also offers mechanical protection and metabolic support, for example, in the form of free fatty acids (FFA), to the adjacent myocardium. Inside-to-outside signalling from the myocardium to the EAT also occurs. For example, natriuretic peptides upregulate adiponectin biosynthesis and possibly induce adipose tissue browning. Lipid peroxidation products generated in states of increased myocardial oxidative stress can diffuse to the surrounding EAT,

increasing adiponectin biosynthesis through the activation of peroxisome proliferator activated receptor- γ (PPAR γ), and adiponectin then exerts antioxidant effects on the myocardium in a protective paracrine loop. In heart failure, inflammatory mediators including IL-6 and tumor necrosis factor (TNF) released from the diseased myocardium can trigger EAT lipolysis, contributing to the cardiac cachexia and decreased EAT volume observed in patients with heart failure. GLUT4, glucose transporter type 4; H₂S, hydrogen sulphide; NO, nitric oxide.

Figure 4. Noninvasive imaging for adipose tissue phenotyping. Adipose tissue dysfunction is implicated in a wide range of cardiometabolic abnormalities; however, adipose tissue characterization in the clinical setting is limited to measurement of simple anthropometric indices, predominantly BMI. Unfortunately, the BMI does not capture important adipose tissue features, such as distribution, biology, and overall body fat composition. Alternative anthropometric measurements, such as Waist-to-Hip ratio (WHR) and Waist-to-Height ratio (WHtR) are more appropriate obesity indices of cardiometabolic risk than BMI, but still do not provide important information on adipose tissue biology and visceral distribution. Several widely-used clinical imaging modalities can be employed to provide this information, with each modality having its relative advantages (green box) and limitations (red box) compared with the others. **a** | Ultrasound is a safe and widely available method to assess thickness of superficial adipose tissue layers, such as femoral, abdominal, and subcutaneous adipose tissue (SAT), or even epicardial adipose tissue (EAT). However, ultrasound is subject to operator-dependent variability and cannot provide information on most visceral adipose tissue (VAT) depots. These limitations are overcome by CT imaging and MRI. **b** | CT has high accuracy and reproducibility for quantitative adipose tissue characterization and can also provide qualitative information by means of adipose tissue CT signal attenuation. CT can be combined with angiography of vascular beds, allowing tracking and characterization of perivascular adipose tissue (PVAT). Novel PVAT characterization algorithms on coronary CT angiography can extract information on coronary inflammation. **c** | MRI is associated with longer acquisition times, higher costs, and less availability, but avoids ionising radiation exposure and can provide functional information through combination with, for example, proton spectroscopy. **d** | MRI and CT can be combined with PET to extract functional information, for example, on adipose tissue inflammation or browning, by the administration of appropriate radiotracers, most commonly ¹⁸F-fludeoxyglucose, at the cost of increased radiation exposure, long acquisition times, and often poor spatial resolution.

Table 1. Adipose tissue products and their effects on the cardiovascular system.

Adipose tissue product	Levels versus healthy conditions		Effects on the cardiovascular system ^a	Examples of suggested mechanisms ^a
	Obesity	IR/DM		
Adipokines				
Activin A	↑/-	↑/-	Pro-fibrotic and ↑ IR	• Promotes fibrosis (might be mediated by angiotensin II), which is linked to arrhythmogenicity
Adiponectin	↓	↓	Anti-oxidant, anti-inflammatory, and ↓ IR	• ↓ NF-κB signalling • ↑ AMPK and AKT signalling • ↓ NADPH oxidase activity (↓ p47 ^{phox} /RAC1 translocation) • ↑ eNOS phosphorylation and coupling (↑ BH ₄ bioavailability)
Angiotensinogen/angiotensin II/aldosterone	↑	↑	Pro-oxidant, pro-inflammatory, and pro-fibrotic	• ↑ NF-κB signalling (angiotensin II) • ↑ NADPH oxidase activity (angiotensin II)
Apelin	↑	↑	Pro-oxidant and pro-inflammatory	• ↑ NADPH oxidase activity (↑ subunit expression)
Chemerin	↑	↑	Pro-oxidant and pro-inflammatory	• ↑ eNOS expression, but ↑ eNOS uncoupling
Leptin	↑	↑	Pro-oxidant and other pleiotropic effects	• ↑ NADPH oxidase activity (↑ p47 ^{phox} activation) • ↑ Mitochondrial ROS generation • ↑ eNOS expression
Omentin 1	↓	↓	Anti-oxidant, anti-inflammatory, and ↓ IR	• ↓ NADPH oxidase activity (↓ p47 ^{phox} activation) • ↓ TNF-induced VCAM1 expression
Resistin	↑	↑	Pro-oxidant, pro-inflammatory, and ↑ IR	• ↑ NADPH oxidase activity (↑ p47 ^{phox} activation) • ↓ eNOS expression
Retinol-binding protein 4	↑/-	↑/-	Pro-oxidant, pro-inflammatory, ↑IR	• ↑ NF-κB signalling • ↑ NADPH oxidase activity • ↑ Cell-adhesion molecules (such as VCAM1)
Visfatin	↑/-	↑/-	Pro-oxidant, (pro-inflammatory)	• ↑ NF-κB signalling • ↑ NADPH oxidase activity • ↑ Cell-adhesion molecules (such as VCAM1)
Pro-inflammatory cytokines and chemokines				
For example, TNF and IL-6	↑	↑	Pro-oxidant, pro-inflammatory, and ↑ IR	• ↑ NADPH oxidase activity • ↑ Cell-adhesion molecules (such as VCAM-1)
Non-coding RNAs				
microRNAs	↑/-/↓	↑/-/↓	Regulation of inflammation, and fibrosis, and VSMC	• Repress protein production through binding and destabilization of specific mRNAs

			activation and migration	
<i>Gaseous messengers</i>				
Hydrogen sulphide	↓	↓	Anti-oxidant, anti-inflammatory, vasodilatory, and pro-angiogenic	For example, activates ATP-regulated potassium channels, which promotes vasorelaxation
Nitric oxide	↓	↓	Anti-inflammatory and vasodilatory	<ul style="list-style-type: none"> • ↑ cGMP in VSMCs, which leads to ↑ PKG and to vasorelaxation • Further immunomodulatory effects
<i>Reactive oxygen species</i>				
Hydrogen peroxide	↑/-	↑/-	Pro-oxidant, pro-inflammatory, vasoactive, and also involved in signal transduction	H ₂ O ₂ promotes vasorelaxation through an endothelium-independent mechanism
<i>Other products</i>				
Antibodies	Not known	Not known	Anti-atherogenic or pro-atherogenic	For example, PVAT-residing B ₁ cells produce IgM targeting oxidation-specific epitopes on LDL.
PAME	Not known	Not known	Vasodilatory	For example, activates voltage-dependent potassium channels, which leads to vasorelaxation

^aThe list of effects and mechanisms is not exhaustive, but rather aims to provide an overview of the major cardiovascular effects of adipose tissue-derived products. –, no change; AKT, RAC-alpha serine/threonine-protein kinase; BH₄, tetrahydrobiopterin; cGMP: cyclic guanosine monophosphate; DM, diabetes mellitus; eNOS, endothelial nitric oxide synthase; IgM, immunoglobulin M; IR, insulin resistance; NADPH, nicotinamide adenine dinucleotide phosphate; NF-κB: nuclear factor-κB; PAME, palmitic acid methyl ester; PKG: protein kinase G; PVAT: perivascular adipose tissue; ROS, reactive oxygen species; TNF, tumour necrosis factor; VCAM1, vascular cell adhesion molecule 1; VSMC, vascular smooth muscle cell.

Table 2. Non-invasive imaging modalities for adipose tissue phenotyping

Imaging method	Methodology	Availability	Cost	Radiation	Spatial resolution	Operator dependence	Scanning time	Strengths	Limitations
Dual energy X-ray absorptiometry (DEXA)	Measures fat mass by calculating the differential absorption of two X-ray beams at different energy levels.	+++	+	+	+	+	+	Rapid, low-cost, yet crude assessment of body composition and total and/or visceral fat mass.	Cannot easily provide detailed information on adipose tissue distribution and specific adipose tissue depots.
Ultrasound	Adipose tissue appears as a hypoechoic space or structure and can be defined based on adjacent structures and probe orientation.	+++	+	-	+	+++	+	Easy, low-cost method to measure the thickness of accessible adipose tissue depots (such as abdominal and gluteal SAT, and EAT). Measurements can be collected from routine clinical scans (for example, transthoracic echocardiography).	Relies traditionally on 2D (for example, thickness) rather than 3D measurements (such as volumes). Operator dependent.
CT imaging	Computer-processed combinations of 3D X-ray images, producing cross-sectional images of the body. Application of standardized attenuation thresholds (for example, -190 to -30 Hounsfield Units) allows the segmentation of adipose tissue structures.	+++	++	++	+++	+	+	Widely used imaging method with numerous clinical indications and high spatial resolution. Excellent segmentation algorithms for adipose tissue distribution characterization. Can be combined with CT angiography to link perivascular fat characteristics with vascular and cardiac pathology.	Radiation exposure (varies with different protocols). Relies on heavily used equipment.

MRI	Various pulse sequences can be used to separate adipose tissue from non-adipose tissue structures (such as T1-weighted and T2-weighted imaging, chemical (frequency)-selective imaging, and chemical-shift encoded imaging)	+	+++	-	++	+	++	Excellent technique that avoids radiation exposure and provides 3D data on adipose tissue distribution. Chemical-shift water-fat MRI or combination with proton spectroscopy can provide additional functional characterization such as on adipose tissue browning.	Expensive technique, with limited availability and long scanning time. Requires appropriate protocol adjustments to acquire accurate adipose tissue measurements.
PET-CT and PET-MRI	Quantifies radiotracer uptake in a volume of interest, guided by co-registration of the PET images with CT or MRI data.	+	+++	+++	+	+	+++	Hybrid PET-CT and PET-MRI imaging combines the excellent spatial resolution and characterization of CT and MRI imaging with functional information on inflammatory and metabolic activity of adipose tissue by means of radiotracer uptake (such as ¹⁸ F-fluorodeoxyglucose).	Expensive technique with limited availability, poor spatial resolution, and high radiation exposure.

+, low; ++, medium; +++, high.

Glossary

Visceral adipose tissue (VAT)

Adipose tissue surrounding the visceral organs in the thorax and abdomen, including fat in the omental and mesenteric peritoneal folds (omental/mesenteric adipose tissue), around the kidneys in the retroperitoneal space (perirenal adipose tissue), as well as epicardial, pericardial, and other depots.

Epicardial adipose tissue (EAT)

The adipose tissue layer that lies between the surface of the heart and the visceral pericardium.

Pericardial adipose tissue (PAT)

Adipose tissue layer located on the external surface of the parietal pericardium.

White adipose tissue (WAT)

The predominant adipose tissue type found in the human body, which is responsible for energy storage in the form of triglycerides and energy supply to peripheral tissues through regulated release of free fatty acids.

Brown adipose tissue (BAT)

A distinct, metabolically active adipose tissue phenotype, found predominantly in the interscapular and supraclavicular regions in humans, and involved in thermoregulatory thermogenesis.

Beige adipose tissue

Also known as brite adipose tissue; an inducible, brown-like adipose tissue phenotype, which is normally found interspersed in white adipose tissue depots.

Ectopic fat

Fat stored in tissues other than the adipose tissue that normally contain small amounts of fat, such as the heart, liver, and muscles.

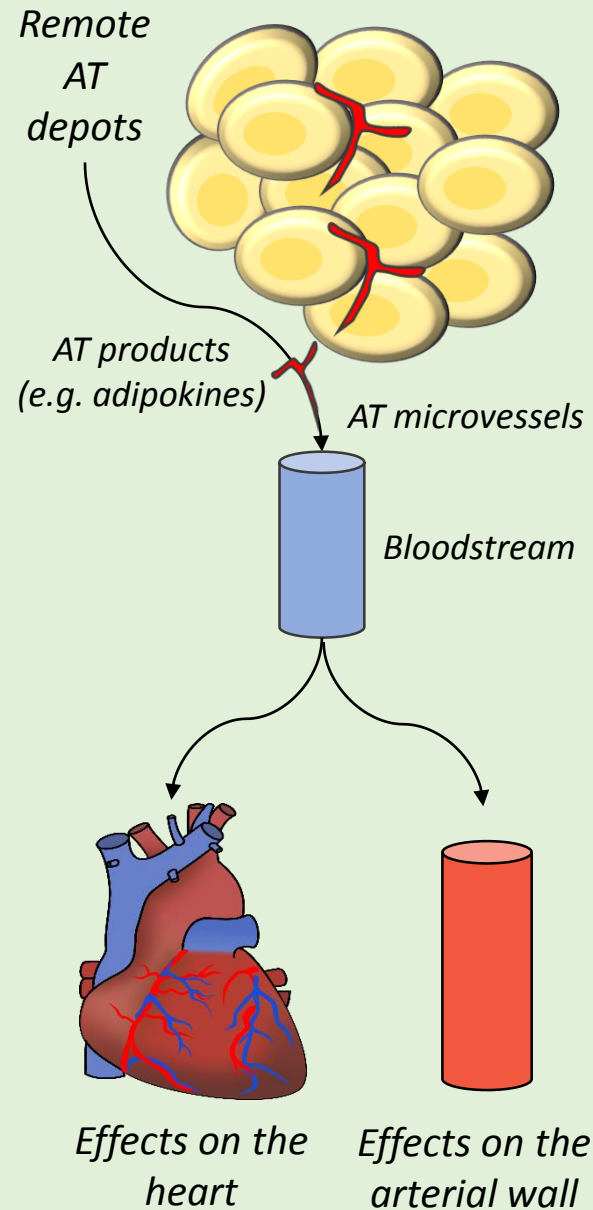
Adipocytokines

A range of bioactive molecules secreted by various cell types found in the adipose tissue (such as adipocytes and stromal cells) that exert autocrine, paracrine, and endocrine effects on both the adipose and peripheral tissues.

Perivascular adipose tissue (PVAT)

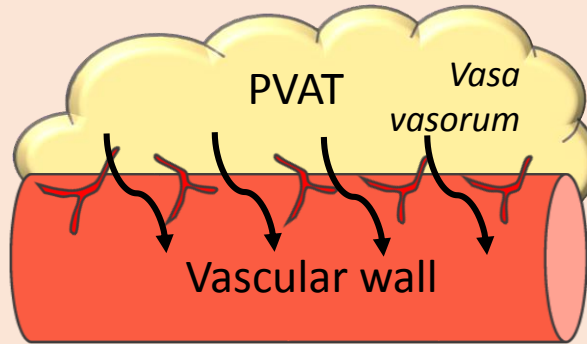
Adipose tissue surrounding the vessels and is often contiguous to the outer adventitial layer.

Endocrine signalling

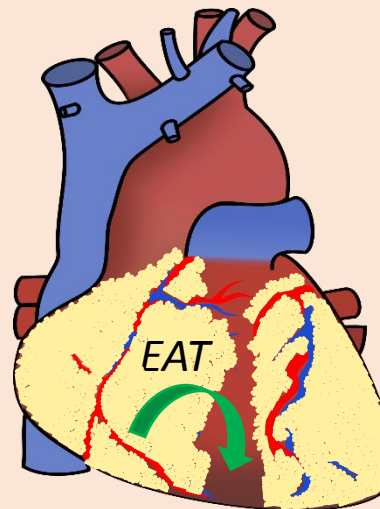


Paracrine signalling

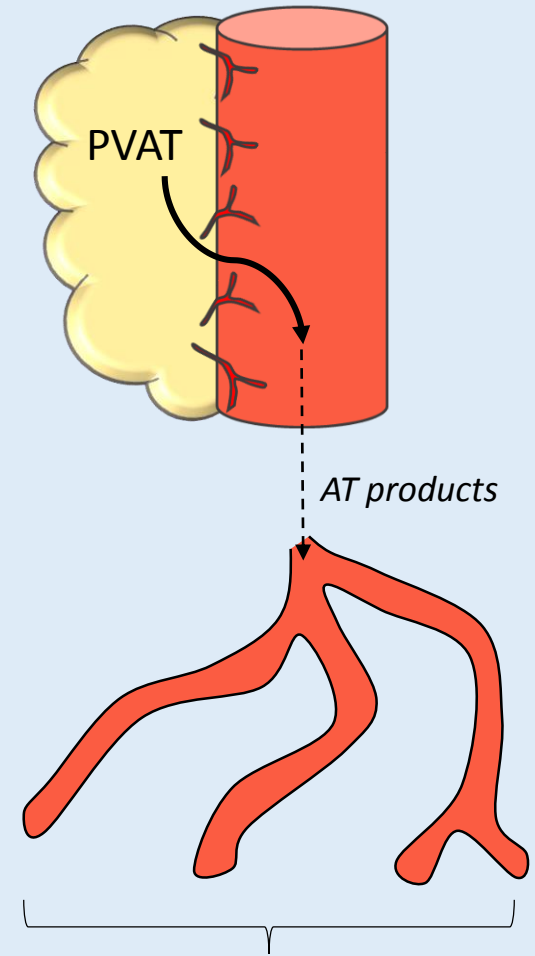
a. PVAT → Vascular wall



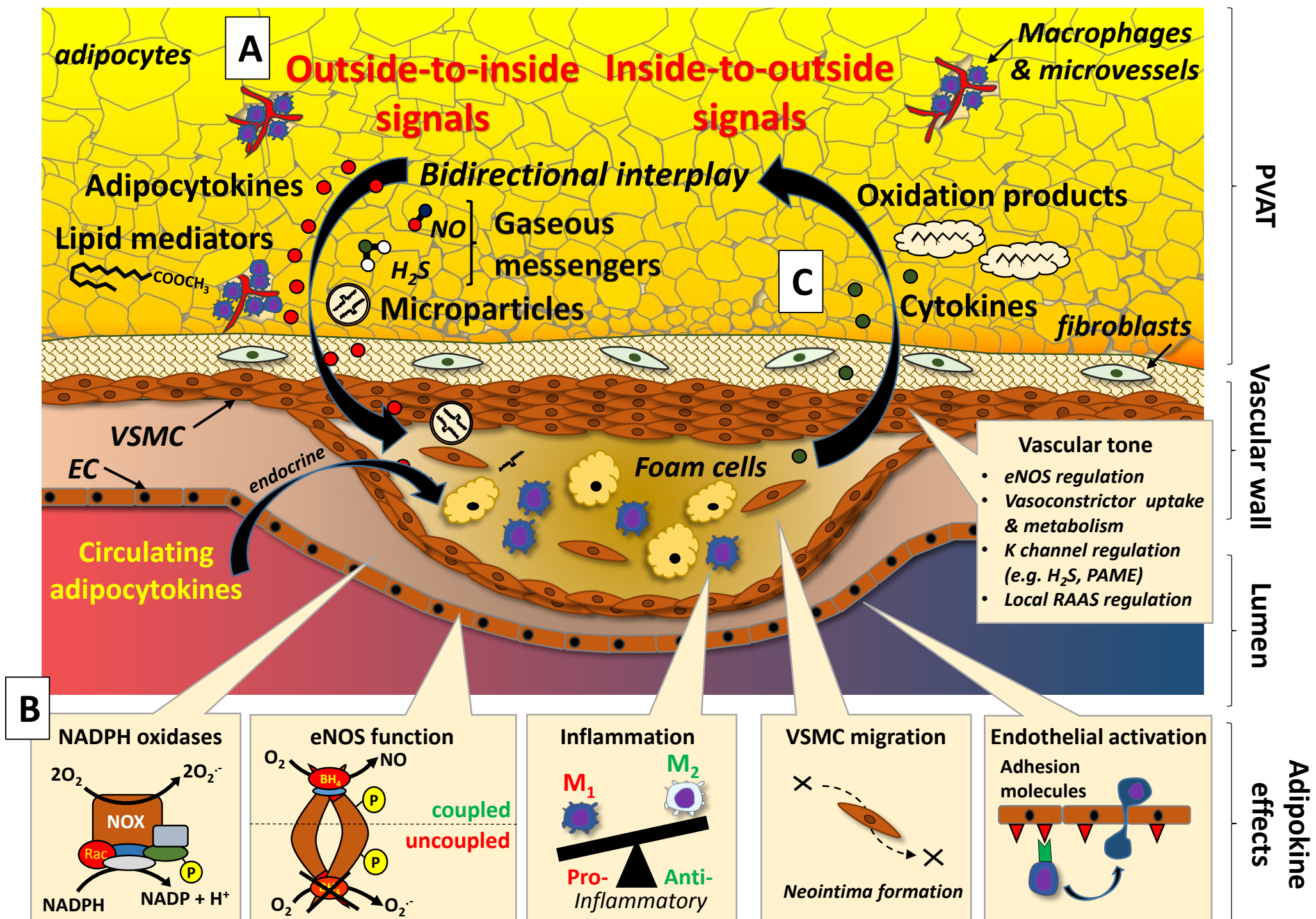
b. EAT → Heart/Cardiomyocytes

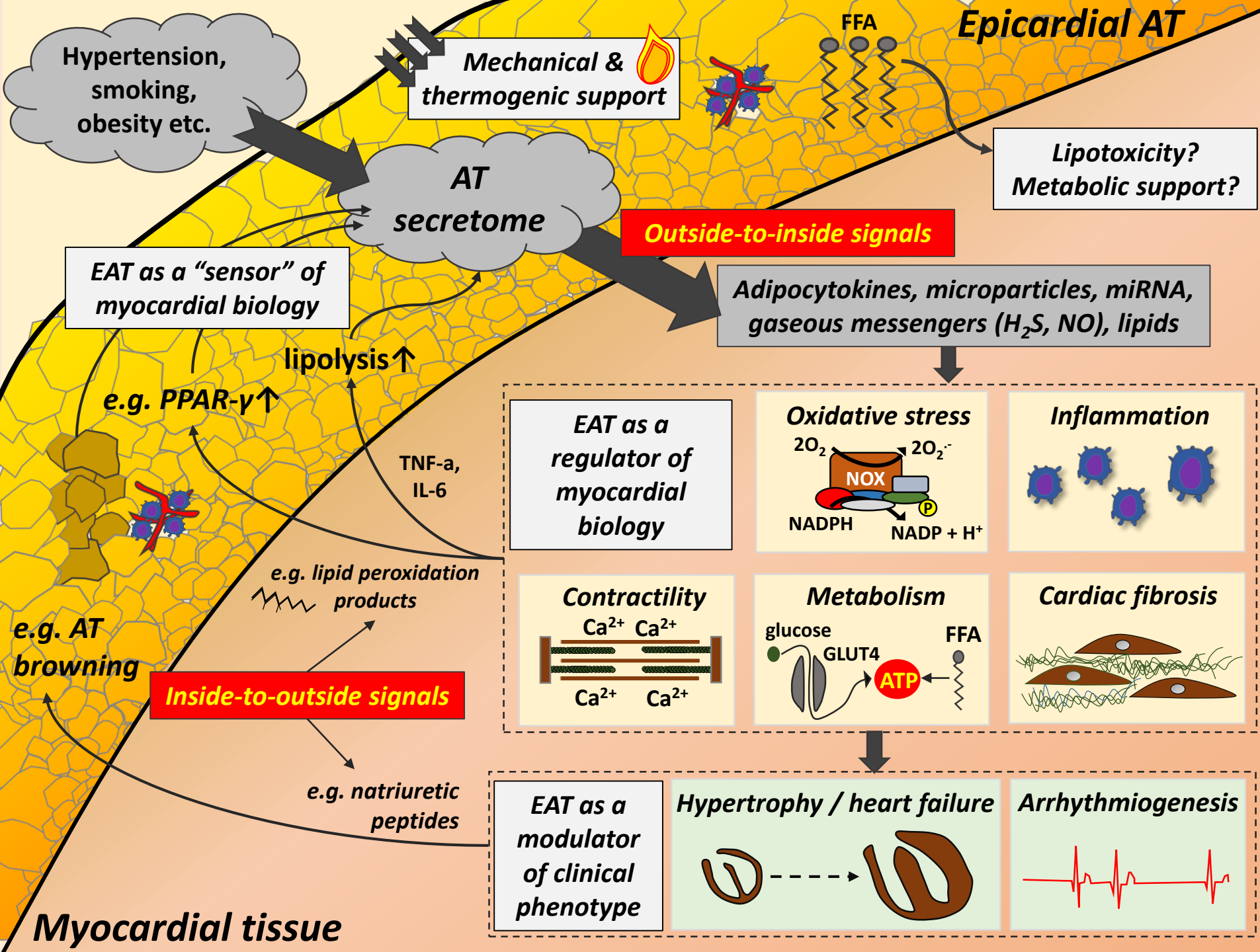


Vasocrine signalling

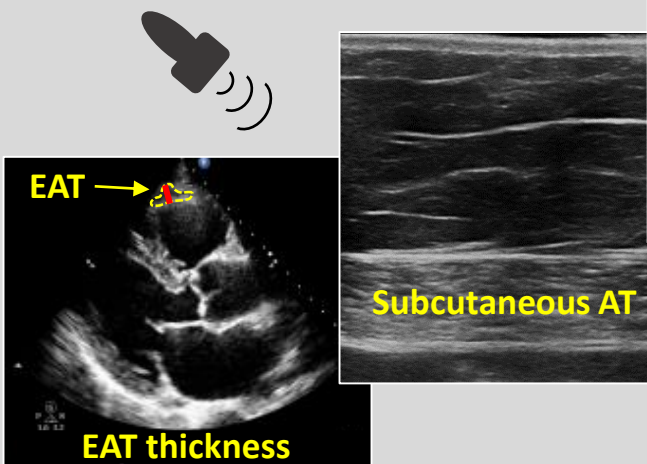


Regulation of entire vascular beds





A. Ultrasound

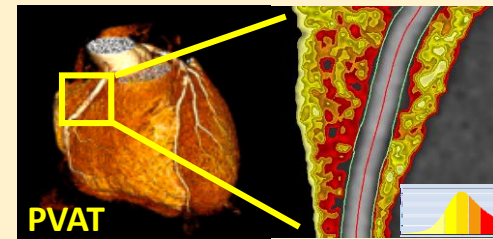
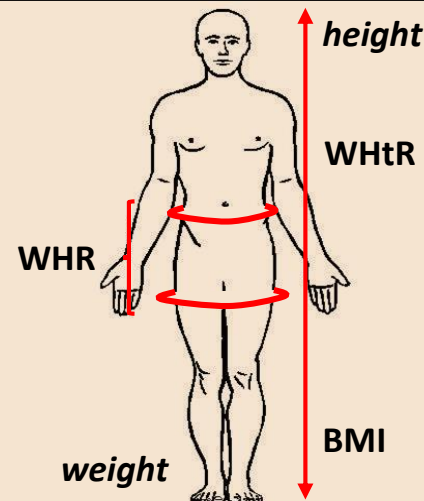


- + ↓cost, ↑ availability, ease of use, no radiation
- low reproducibility, operator-dependent, relies on 2-dimensional measurements

B. Computed tomography (CT)



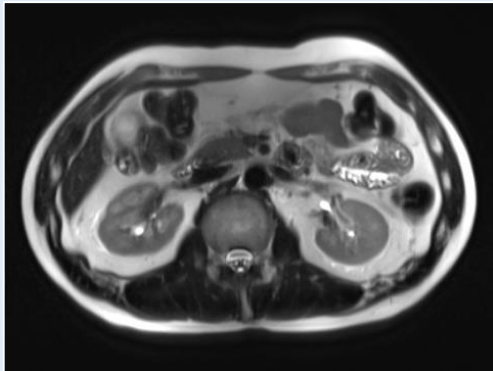
How to characterise AT in clinical practice?



PVAT as a sensor of coronary inflammation

- + ↑accuracy/reproducibility/resolution, widespread use, +angiography, ↓cost
- Radiation

C. Magnetic Resonance Imaging

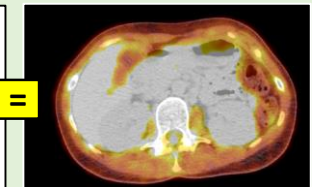
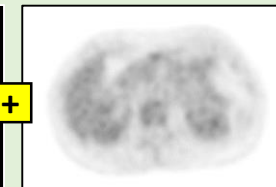


- + accurate volumetric quantification, no radiation, can be combined with spectroscopy to detect e.g. AT browning
- costly, long acquisition times, limited availability

D. PET-CT/MRI



e.g. ^{18}F -FDG



- + extraction of functional information (e.g. inflammation or AT browning), continuous development of novel radiotracers
- High radiation dose, costs, limited availability, poor spatial resolution