Perivascular adipose tissue and coronary atherosclerosis

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ABSTRACT

Adipose tissue (AT) is no longer viewed as a passive, energy-storing depot, and a growing body of evidence supports the concept that both quantitative and qualitative aspects of AT are critical in determining an individual's cardiometabolic risk profile. Among all AT sites, perivascular AT (PVAT) has emerged as a depot with a distinctive biological significance in cardiovascular disease given its close anatomical proximity to the vasculature. Recent studies have suggested the presence of complex, bidirectional paracrine and vasocrine signalling pathways between the vascular wall and its PVAT, with far-reaching implications in cardiovascular diagnostics and therapeutics. In this Review, we first discuss the biological role of PVAT in both cardiovascular health and disease, highlighting its dual pro-atherogenic and anti-atherogenic roles, as well as potential therapeutic targets in cardiovascular disease. We then review current evidence and promising new modalities on the non-invasive imaging of epicardial AT and PVAT. Specifically, we present how our expanding knowledge on the bidirectional interplay between the vascular wall and its PVAT can be translated into novel clinical diagnostics tools to assess coronary inflammation. To this end, we present the example of a new computed tomography-based method that tracks spatial changes in PVAT phenotype to extract information about the inflammatory status of the adjacent vasculature, highlighting the numerous diagnostic and therapeutic opportunities that arise from our increased understanding of PVAT biology.

Keywords: Perivascular AT; epicardial AT; pericoronary AT coronary atherosclerosis; computed tomography angiography; attenuation; fat attenuation index, FAI

INTRODUCTION

Obesity, traditionally defined as a body mass index (BMI) ≥30 kg/m^2, represents one of the main preventable causes of morbidity and mortality in Western societies.[1] However, recent large-scale epidemiological studies have questioned the exact nature of this association, revealing a non-linear, U-shaped association between BMI and all-cause mortality in patients with established cardiovascular disease.[2] This phenomenon, often described as "obesity paradox", highlights the complex biology of adipose tissue (AT) and its variable effects on the cardiovascular system. BMI, despite its widespread use, fails to take into account variations in AT quality and distribution, which are now established as key determinants of its cardiometabolic effects.[3] Depot-specific differences in the ability of AT to store lipids as well as its secretome profile are important in understanding the complex association of AT with cardiovascular disease.[2]

Given its anatomical proximity to the vascular wall, perivascular AT (PVAT) has been identified as a key player in both cardiovascular homeostasis and disease.[4] Contrary to distant AT depots that regulate cardiovascular biology by contributing to a circulating pool of bioactive adipocytokines, PVAT is able to directly modulate key signalling pathways in the vascular wall and myocardium through paracrine and vasocrine routes.[5] More importantly, we have recently shown that the communication between the vascular wall and PVAT is bi-directional. For instance, locally released inflammatory mediators and/or oxidation products from the diseased vessel can directly modify the phenotype of perivascular adipocytes.[6-8]

In this review, we first describe the anatomy and physiological functions of PVAT, identifying the need for a universal definition that would reflect its distinct biological and imaging characteristics. Next, we discuss the mechanisms by which dysfunctional AT contributes to cardiovascular disease, highlighting the bidirectional communication between the vascular wall and its PVAT, as

well as promising therapeutic targets related to this axis. Finally, we discuss the diagnostic and possible prognostic value of non-invasive imaging of PVAT, focusing on a recent paradigm shift in our understanding of PVAT as a sensor of vascular inflammation.

The biological role of PVAT in health and disease

Building a universal definition for PVAT

Given the absence of an established definition, PVAT is traditionally, and rather crudely, defined as any AT surrounding a blood vessel. This includes peri-aortic fat, as well as organ-specific fat depots located close to major vessels, including the epicardial, pericardial, and peri-renal AT depots.[4] As with any AT depot, PVAT is composed of various cell types such as adipocytes, pre-adipocytes, and mesenchymal stem cells, embedded in a matrix that is invested in microvessels.[4] In humans, PVAT is contiguous with the adventitial layer of the large vessels wall, but it is essentially integrated into the wall of small vessels; it contains predominantly white AT in resistance vessels, whereas large vessels are characterized by both brown and white ATs.[4 5] Of all PVAT sites, coronary PVAT is the most widely studied depot, given its close anatomical proximity to the coronary vessels. Nevertheless, the absence of a clear anatomical border has resulted in highly heterogeneous definitions of coronary PVAT in the literature. We have recently proposed a definition of PVAT as any AT within a radial distance from the outer vessel wall equal to the diameter of the adjacent coronary vessel.[7] This definition is based on a series of histological and gene expression studies that have revealed changing patterns in AT phenotype with increasing distance from the vascular wall, as a result of complex, paracrine vessel-PVAT interactions.[7] In order to better understand these, a review of the physiological functions of PVAT in health and disease is necessary.

Physiological function of PVAT in health

While AT was initially considered to provide exclusively mechanical, metabolic (energy supply and glucose homeostasis) and thermostatic support to the vasculature, in the recent years it has become clear that AT, including PVAT, is also responsible for the secretion of various bioactive molecules, collectively known as adipocytokines. The exact source of these molecules may vary (e.g. cytokines are predominantly produced by inflammatory residing cells in AT, adipokines such as adiponectin as produced mainly by the adipocytes themselves), but they are all critical for the regulation of vascular physiology, including vascular redox state, vascular tone, and endothelial function.[4] In normal conditions, PVAT exerts anticontractile, anti-inflammatory, and anti-oxidant effects.[5 9 10] For instance, regulation of vascular tone is dependent on the continuous release of PVAT-derived relaxing factors that enhance vasodilatation via both endothelium-dependent and -independent mechanisms.[11 12] Beyond their effects on vascular tone regulation, adipokines, such as adiponectin and omentin, also exhibit anti-inflammatory and anti-oxidant properties by inhibiting nuclear NF-kB (nuclear factor kappa beta) signalling and NADPH (nicotinamide adenine dinucleotide phosphate)-oxidase activity and restoring endothelial nitric oxidase synthase (eNOS) coupling.[9 10 13]

Obesity-induced PVAT remodelling

In response to excessive caloric intake, AT is forced to expand through adipocyte hyperplasia and/or hypertrophy. This may eventually progress to adipocyte dysfunction and apoptosis, with subsequent inflammatory cell infiltration, late capillary rarefaction and, ultimately, fibrosis.[14] This AT remodelling generates a systemic chronic, low-grade inflammatory state as a result of a shift

in the adipocyte phenotype from a protective profile to an imbalanced production of pro-inflammatory, pro-oxidant and pro-fibrotic adipokines, such as leptin, resistin and visfatin.[3] Of note, these biological variations are depot-specific. Genome,[15 16] transcriptome,[17] proteome,[18] and mriRNome[19]-wide expression analyses have identified significant phenotypic differences between EAT and subcutaneous AT (SAT) in CAD patients. Compared to SAT, EAT is characterised by higher expression of pro-inflammatory (tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), interleukin 1- β (IL1-β)), pro-oxidant (NADPH-oxidase, superoxide dismutase-2, catalase, glutathione S-transferase P, protein disulphide isomerase) and angiogenic (vascular endothelial growth factor receptor 1, endothelin 1, angiotensin II receptor 1)-regulatory genes as well as greater infiltration by immune cells, particularly M1 pro-inflammatory macrophages.[16 18 20] Nevertheless, EAT itself is a rather heterogeneous depot, with distinctive transcriptomic signatures around pericoronary, periatrial, and periventricular sites,[17] highlighting the complex, paracrine interactions between EAT, the coronary vessels and myocardium. A representative summary of the differentially expressed genes or proteins in EAT is presented in Table 1.[15-19]

Vascular disease-induced PVAT remodelling

We have previously demonstrated that the communication between perivascular adipocytes and the vascular wall is bi-directional, with signals arising from the cardiovascular system modulating adipocyte differentiation and function.[6-10] Specifically, upregulation of adiponectin expression in PVAT in advanced stages of disease may represent a protective mechanism triggered by increased oxidative stress in the adjacent vasculature (e.g. through lipid peroxidation products that diffuse from the vessel into the surrounding PVAT activating PPARγ [peroxisome proliferator-activated receptor gamma] signalling). In remote AT depots, adiponectin biosynthesis is under the regulation

of circulating brain natriuretic peptides, a biomarker of heart failure.[8] This presence of dynamic, phenotypic (morphological and functional) changes in fat composition as a result of its interactions with the cardiovascular system is further supported by experimental studies in mice and pigs. In a mouse model, balloon- or wire-induced vascular injury rapidly induced inflammation and perturbed adipokine gene expression in PVAT.[21] Similarly, in a porcine model of drug-eluting stent-induced coronary vasoconstriction, PVAT inflammation, as assessed in vivo and in vitro by 18F-fluorodeoxyglucose positron emission tomography (18F-FDG PET), was enhanced at the stent edges compared with control sites.[22]

PVAT as a host of therapeutic targets

As a result of our increasing understanding of the causal involvement of PVAT in cardiovascular disease pathogenesis, a range of therapeutic targets have been proposed. Potential strategies include the modulation of adipocytokine-mediated signalling pathways through direct administration of adiponectin or specific targeting of its receptors (AdipoR1 and 2).[8] Another approach is the modulation of more upstream pathways involved in insulin sensitivity and adiponectin biosynthesis regulation, such as PPARγ, using thiazolidinediones.[23] Furthermore, expanding evidence now confirms that both glucagon-like-peptide 1 agonists and dipeptidyl peptidase-4 inhibitors increase adiponectin expression and macrophage polarization, while also promoting AT browning.[23 24] Moreover, AT is a source of angiotensinogen contributing to activation of renin-angiotensin-aldosterone system (RAAS), which can be blocked by the widely used angiotensin-converting enzyme inhibitors and angiotensin-2-receptor blockers.[13 23] The extent to which these pathways can be modulated in the paracrine PVAT-vessel interactions as well as their potential cardiovascular benefit remain unclear. Scientific advancements in delivery

methods that specifically target AT may boost research in this field and lead to novel treatment options in cardiovascular therapeutics.[25]

PVAT imaging for cardiovascular risk stratification

Based on both its biological and close anatomical relationship with the coronary vessels, coronary PVAT imaging may provide useful information for cardiovascular risk stratification. Nevertheless, given the absence of dedicated analysis algorithms, PVAT imaging in most studies has been limited to the crude analysis of total EAT. Indeed, EAT can be easily visualized by routine transthoracic echocardiography and its thickness in the anterior surface of the right ventricle can be measured in a safe and easy manner.[26] However, the amount of EAT is more accurately and reproducibly quantified by cardiac computed tomography (CT) or magnetic resonance imaging.[27] Most studies have relied on non-contrast CT scans for EAT segmentation, however coronary CT angiography provides an optimal method of assessing not only the coronary anatomy, but also specific features of coronary PVAT. The relative advantages and limitations of the available imaging methods to assess epicardial and pericoronary AT depots are presented in Table 2.

EAT volume and coronary atherosclerosis

Several large-scale epidemiological studies conducted in community-based cohorts have explored the importance of EAT volume, such as the Framingham Heart Study,[28 29] MESA (Multi-Ethnic Study of Atherosclerosis),[30] Heinz Nixdorf Recall Study,[31 32] and Rotterdam Study (Table 3).[33] These general population cohorts composed of asymptomatic low-risk subjects demonstrated that EAT volume (measured on non-contrast CT scans) was associated with the presence of ischaemic heart disease,[29] incidence of major adverse cardiovascular events (MACE),[32] coronary

calcification,[28 30] and calcium progression.[31] Furthermore, among participants recruited from hospital registries with low-to intermediate-cardiovascular risk (reflecting the current indications for cardiac CT), higher EAT volumes were positively associated with the presence of coronary stenosis,[34] myocardial ischaemia,[35] calcified,[36] non-calcified coronary plaques,[37] as well as high-risk plaque features, such as low-attenuation plaque and thin fibrous cap. However, in the CORE320 (Coronary Artery Evaluation using 320-row Multidetector Computed Tomography Angiography and Myocardial Perfusion) study, Tanami *et al*.[38] did not find an independent association between EAT volume and either obstructive CAD, myocardial ischaemia on single photon-emission computed tomography (SPECT) or coronary calcification. Of note, 27% of CORE320 study population had previously undergone percutaneous coronary intervention, and therefore represented a high-risk population.

It should be highlighted that even though EAT volume has been independently associated with ischaemia and coronary calcification in cross-sectional analyses,[28-30] as well as with the prospective incidence of adverse events, such as myocardial infarction,[32] its relationship with CAD may change over the natural history of the disease in response to signals arising from the coronary vasculature, as well as pharmacological and lifestyle interventions, such as weight loss reduction after bariatric surgery,[39] exercise[40] and low-calorie diet.[41] Interestingly, in the SMART (Secondary Manifestations of ARTerial disease) study, Franssens *et al*.[42] found that low EAT attenuation on CT was associated with an adverse metabolic profile, and this association was independent of EAT volume, indicating that fat quality measures might add complementary information to that provided by EAT quantity.

EAT quality and coronary atherosclerosis

While qualitative characterization of a given AT depot requires direct access to tissue biopsies, non-invasive imaging modalities provide a more practical approach to AT phenotyping in the clinical setting. AT inflammation, a hallmark of dysfunctional AT, can be assessed using PET-CT and has been used to link the metabolic activity of EAT with coronary inflammation (assessed by ^{18}F-FDG uptake).[43] However, PET-CT is limited by poor spatial resolution, and significant background noise due to myocardial uptake of the radiotracer. Simple cardiac CT can provide a qualitative assessment of a given AT depot by means of its attenuation. In order to create a standardised CT-based approach to the qualitative analysis of PVAT, we have recently described a novel metric, namely the Fat Attenuation Index (FAI), that provides a numerical index of AT composition.[7] FAI was defined as the standardised average attenuation of the AT in a region of interest (within the prespecified window of −190 to −30 Hounsfield Units [HU]) and was inversely associated with adipocyte size and differentiation.[7] In the past, several studies have assessed the association of EAT attenuation with the overall cardiovascular risk profile and CAD. In the SMART study, Franssens *et al.* [44] found a negative association between EAT attenuation and age, BMI, waist circumference, visceral abdominal AT, fasting glucose and insulin resistance, and importantly, these associations were independent of EAT volume, highlighting the different type of information provided by the qualitative AT assessment. In the same cohort, lower EAT attenuation was also associated with coronary artery calcification in men.[44] Similarly, in 609 asymptomatic low-to intermediate-risk patients, Abazid *et al.*[45] observed a negative correlation between EAT attenuation and coronary calcification independent of EAT volume. In contrast, in a cross-sectional analysis of acute myocardial infarction patients and stable CAD controls, Mahabadi *et al.*[27] observed a positive association between EAT attenuation and type I acute

myocardial infarction, while Hell *et al.*[35] did not report a link between EAT attenuation and myocardial ischemia on SPECT. These contradicting results may be explained by a small sample size, the variable nature of the study population, as well as methodological limitations, such as selection bias, reverse causality and the presence of confounders that were not taken into account. But the most critical limitation of these studies[27 35 44 45] remains the analysis of EAT as a homogeneous depot, which ignores the biologically important phenotypic variability of PVAT versus non-PVAT depots in the human heart.[17]

PVAT image phenotyping for detection of cardiovascular disease

We have recently developed, for the first time, a detailed analysis method of coronary PVAT as a sensor of coronary inflammation and vascular disease, which can be calculated on routine coronary CT angiograms.[7] This followed the observation that in the presence of coronary inflammation, the release of pro-inflammatory mediators from the vascular wall into the surrounding PVAT blocks the differentiation of perivascular pre-adipocytes into mature, lipid-laden adipocytes.[7] In patients with CAD, this results in a pericoronary gradient of lipid accumulation and a shift from a greater to a lesser lipophilic content (moving closer to the vascular wall), as evidenced by histological and gene expression analysis of paired EAT biopsies attached to the right coronary artery and 20 mm away (Figure 2A).[7] This gradient in adipocyte size and lipid content correlates with a gradient in the CT-measured attenuation (FAI) of pericoronary/epicardial fat from more negative (away from the vascular wall) to less negative Hounsfield Unit values (closer to the vascular wall), which can now be detected using this novel three-dimensional analysis algorithm (Figure 2B). Following extensive validation of this biomarker, we confirmed that perivascular FAI (FAI_{PVAT}) is significantly increased around the coronary vessels of patients with CAD compared to healthy

controls (Figure 3), as well as around the culprit lesions of acute myocardial infarction patients versus stable lesions from the same patients or patients with stable CAD.[7] Of note, FAI_{PVAT} appears to track longitudinal changes in coronary inflammation, as evidenced by a significant decrease in FAI_{PVAT} around the culprit lesions in acute myocardial infarction patients five-week after the acute, baseline scan.[7]

Non-invasive detection of coronary inflammation by means of FAI_{PVAT} in low-to intermediate-risk subjects could enable the early detection of subclinical CAD, especially among high-risk individuals without visible coronary lesions who are not detected by traditional CT angiography. In patients with established CAD, FAI_{PVAT} could help to assess the inflammatory burden and hence the vulnerability of coronary plaques, identifying those at higher risk of having an acute coronary event and who may benefit from more aggressive medical interventions. To this end, future clinical trials will explore whether PVAT imaging can be used to guide the deployment of expensive therapies targeting inflammation in human atherosclerosis.[46]

Our recent discoveries have been followed by a renewed interest in the non-invasive imaging phenotyping of PVAT. In a per-segment analysis of stable patients with CAD referred for invasive coronary angiography, Marwan *et al*.[47] studied 60 coronary segments by intravascular ultrasound in a total of 29 patients and demonstrated that PVAT attenuation was higher around segments with fibrous or lipid-rich plaques, compared to segments without disease. Nevertheless, no difference was found in the pericoronary PVAT attenuation of fibrous versus lipid-rich plaques. More recently, in a study of 27 patients with vasospastic angina and 13 controls, Ohyama *et al.*,[48] have reported increased adventitial and PVAT inflammation in patients with vasospastic angina, as evidenced by increased PVAT signal on 18F-FDG PET. Other studies have explored the possible association between PVAT and vascular disease in extra-coronary vascular beds. While magnetic

resonance-derived volumetric features of peri-carotid and peri-aortic PVAT in humans may not be correlated with the local presence of vascular disease,[49] CT attenuation of peri-aortic PVAT is positively associated with aortic calcification in a cohort of female patients with systemic lupus erythematosus.[50] These observations further highlight the importance of qualitative over quantitative features in the assessment of human PVAT.

CONCLUSIONS AND FUTURE DIRECTIONS

Thanks to its proximity to the coronary vessels, PVAT has emerged as an AT depot with special interest in the cardiovascular field. PVAT is now known to modify local vascular biology through the secretion of adipokines, which exert a range of paracrine effects on the coronary vessels. Both the phenotype and biological effects of PVAT are under the control of complex regulatory mechanisms, both systemic and local/paracrine. The discovery of a bi-directional interplay between the vascular wall and its PVAT has revealed new pathways with important implications in cardiovascular diagnostics and therapeutics. More recent evidence suggests that PVAT can function as a sensor of coronary inflammation, which can now be detected using a novel CT-derived metric, namely $FAI_{PVAT,}$ at no extra cost, or radiation exposure. This tool represents the first major clinical translation of our expanding knowledge on PVAT biology, and could play an important role in improving cardiovascular risk stratification and identifying individuals that would benefit from an ever expanding range of anti-inflammatory and other targeted therapeutic agents in both primary and secondary cardiovascular disease prevention.

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FIGURE LEGENDS

Figure 1: Interactions between adipose tissue (AT) and the coronary vessels. The AT located between the surface of the heart and the visceral layer of the pericardium is defined as epicardial AT (EAT). Contrary to remote AT depots (e.g. pericardial AT, located outside the pericardium) which may affect cardiovascular biology in an endocrine way through the systemic release of adipokines into the circulation, EAT interacts with the adjacent coronary vessels in a paracrine manner. EAT located in close proximity to the vessels is known as perivascular AT (PVAT), and plays a key role in the regulation of cardiovascular health. It has been long established that PVAT can secrete adipokines (e.g. adiponectin) which diffuse directly to the vascular wall, modifying its biology and phenotype. The nature of these effects depends on the secretome of PVAT, which is in turn regulated by both systemic (e.g. insulin resistance, obesity) and local factors (e.g. vascular redox state and inflammatory status). For instance, while adiponectin has been shown to exert anti-oxidant effects on the vasculature, other adipokines (e.g. resistin, visfatin) are known to promote a pro-oxidant and pro-inflammatory phenotype. More recently, the discovery of "inside-to-outside" signalling pathways has shown that PVAT can also function as a sensor of vascular oxidation and inflammation. In response to inflammatory cytokines (e.g. interleukin-6) and lipid peroxidation products (e.g. 4-hydroxynonenal) released by a diseased vascular segment, local PVAT modifies its composition (decrease in adipocyte size and lipid content) as well as biology (e.g. increased production of adiponectin, which in turn exerts anti-oxidant effects on the vascular wall in a protective loop mechanism).

Figure 2. Perivascular adipose tissue phenotyping to detect coronary inflammation. It has recently been demonstrated that in the presence of exogenous inflammatory stimuli, adipocytes lose their ability to differentiate into large, lipid-laden cells (A, left side) and are instead characterized by decreased cell size, lipid accumulation and poor differentiation status (A, right side). This correlates with a shift in the composition of AT from a greater lipophilic to a greater aqueous content, which correlates with a gradient in the attenuation of AT on computed tomography (CT) more negative to less negative Hounsfield Unit (HU) values. In the case of perivascular AT (PVAT), this signifies that in the presence of vascular disease and inflammation, inflammatory mediators released from the vascular wall can induce a concentric gradient of lipid accumulation (lower lipid content closer to the vessel) (B, left side). By applying novel CT analysis tools on routine coronary CT angiograms, we can now track these three-dimensional changes in PVAT phenotype and use them as a dynamic biomarker of the inflammatory status of the adjacent vessel (B, right side).

Figure 3. Gradient of adipocyte size and fat attenuation index (FAI) around the human coronaries in the presence or absence of coronary atherosclerosis. In paired adipose tissue (AT) biopsies of epicardial AT attached to the right coronary artery (RCA) and ~20 mm away in patients undergoing cardiac surgery, quantification of (A) PPAR-γ, (B) CEBPA, and (C) FABP4 gene expression and (D) adipocyte size demonstrated an in vivo perivascular gradient of adipocyte differentiation and size. (E to G) In a separate group of patients undergoing clinical computed tomography angiography, FAI around the proximal RCA was calculated in concentric, cylindrical 1-mm-thick layers of pericoronary tissue. (H) FAI mapping of PVAT around the RCA. (I) FAI and radial distance from vascular wall in patients with coronary artery disease (CAD) (n = 149)

versus healthy individuals (n = 117) CEBPA: CCAAT/enhancer binding protein (C/EBP) α; FABP4: fatty acid binding protein-4; FAI: fat attenuation index; PPAR-γ: peroxisome proliferator-activated receptor gamma; RCA: right coronary artery. Reproduced with permission from Antonopoulos et al. *Sci Transl Med.* 2017;9(398).

TABLES

Table 1: Overview of experimental studies in human pericoronary adipose tissue (PVAT) and vascular disease.

Authors	Experimental Design	Analysis	Main Findings
Mazurek T., US 2003[15]	42 paired PVAT (around the right coronary artery) and SAT samples in patients with CAD who underwent elective CABG	Genome	• EAT exhibited significantly higher levels of chemokine (MCP-1) and several inflammatory cytokines (IL-1, IL-6, IL-6sR, and TNF-alpha) than SAT • Local inflammatory burden may not correlate with plasma concentrations of circulating cytokines • EAT inflammation was independent of several clinical variables (obesity, diabetes, or chronic therapy with statins or ACE inhibitors).
Chatterjee TK., US 2013[16]	6 paired PVAT (around the left coronary artery artery) and SAT samples collected from human organ donors without diabetes or metabolic diseases	Genome	• 156 upregulated genes in PVAT vs. SAT, 59 associated with angiogenesis, vascular biology or inflammation, which include TNFRSF11B (osteoprotegerin), PLAT, TGFB1, THBS2, HIF1, GATA6, SERPINE1 • 166 downregulated genes in PVAT vs. SAT, 21 associated with vascular and inflammation including ANGPT1, ANGPTL1, and VEGFC
Gaborit B., France 2015[17]	41 paired EAT and SAT samples EAT samples collected from matched patients with CAD and AF from PVAT ("pericoronary" (n=15), periatrial (n=10), peri-right ventricle (n=16))	Transcriptome	• Genes overexpressed in PVAT were implicated in proliferation, O-N glycan biosynthesis, and sphingolipid metabolism • Peri-atrial EAT displayed an atypical pattern with genes implicated in cardiac muscle contraction and intracellular calcium signalling pathways
Salgado-Somoza A., Spain 2010[18]	11 paired EAT and SAT samples in patients with CAD who underwent elective CABG	Proteome	• ROS production was higher in EAT than SAT • Catalase levels were lower in EAT than in SAT • EAT differed from SAT in the post-transcriptional profiles of oxidative stress-related proteins such as PDIA1, GSRP1 and PGAM1
Vacca M., Italy 2015[19]	44 paired EAT and SAT samples from CAD patients (93% with metabolic syndrome) (n=29) and controls (metabolically healthy patients without CAD) (n=15)	Whole genome microarrays miRNA	• miR-103-3p levels aresuppressed in EAT of CAD patients • CCL13 circulating levels were increased in CAD patients

ACE: angiotensin-converting enzyme, AF: atrial fibrillation, AT: adipose tissue, CABG: coronary artery bypass grafting, CAD: coronary artery disease, CCL-13: chemokine ligand 13, EAT: epicardial adipose tissue, GSRP1: glutathione S-transferase P1, PDIA1: protein disulfide isomerase, PGAM1: phosphoglycerate mutase 1, PVAT: perivascular adipose tissue, SAT: subcutaneous adipose tissue, ROS: reactive oxygen species.

Table 2: Imaging modalities for assessing epicardial and pericoronary adipose tissue (PVAT) quantity and quality.

Imaging modality	Fat imaged	Measurements	Advantages	Disadvantages
Transthoracic Echocardiography	• EAT	• *Quantity*: Thickness	• Innocuous • Routinely performed • Ease and quick to obtain • Inexpensive	• Low spatial resolution • 2-D measurement at single point • Poor reproducibility • Limited by the quality of acoustic window and by the presence of pericardial effusion
Non-contrast Computed Tomography	• EAT	• *Quantity*: Thickness, area, volume • *Quality:* Attenuation	• Volumetric • IV contrast administration is not required	• Radiation exposure • PVAT cannot be assessed
Computed Tomography Angiography	•PVAT • EAT	• *Quantity*: Thickness, area, volume • Quality: Attenuation	• Volumetric • High spatial resolution • Offer PVAT assessment	• Radiation exposure • IV iodinated contrast required
Magnetic Resonance Imaging	• PVAT • EAT	• *Quantity:* Thickness, area, volume • *Quality*: Proton density fat fraction	• Volumetric • No radiation exposure • No iodinated contrast • Can be coupled with H^1 spectroscopy	• Limited availability • High cost • Inferior spatial resolution than CT • Time-consuming • Less tolerable by patients
18F-fluorodeoxyglucose PET/CT	• PVAT • EAT	• *Quality*: Inflammatory/metabolic activity measured based on radiotracer uptake	• Functional • High sensitivity	• Radiation exposition • Specificity for inflammation is not clearly defined with all agents • Interference by radiotracer presence in the blood pool and surrounding tissues

CT: computed tomography, EAT: epicardial adipose tissue, FDG: F-fluorodeoxyglucose, IV: intravenous, PET: positron emission tomography, PVAT: perivascular adipose tissue.

Table 3: Overview of studies reporting the association between EAT volume on CT and coronary atherosclerosis.

Authors	Study design	Study Population	No. of Subjects	Male (%)	Age Mean±SD (Years)	CAD Outcomes	Main Findings	Variables Included in the Multiple Models	Quality MINORS Score
A. General Population-based Studies									
i) Cross-sectional associations									
Mahabadi A.A. et al. US 2009[29]	Cross-sectional	Framingham Heart Study	1267	46	60±9	CHD (MI, stable or unstable angina), stroke (ischaemic or haemorragic), intermittent claudication, congestive heart failure	• EAT volume was associated with cardiovascular disease independently of BMI and WC, but not after adjustment for traditional cardiovascular risk factors • There was no significant interaction with gender	Age, gender, BMI, WC + systolic blood pressure, hypertensive medication, diabetes, total/HDL cholesterol lipid treatment, smoking, alcohol, menopausal status, and hormone replacement therapy	14 (out of 16)
Rosito, G. et al., US 2009[28]	Cross-sectional	Framingham Heart Study	1155	45	W: 63±9 M: 63±9	CAC	• There was an independent correlation between EAT volume and CAC • A significant interaction with gender was found with EAT being associated with a more adverse risk factor profile in females than males	Age, gender, systolic blood pressure, hypertensive medication, diabetes, total/HDL cholesterol lipid treatment, smoking, alcohol, menopausal status, and hormone replacement therapy + BMI, VAF and WC	14 (out of 16)
McClain, J. et al., US 2013[30]	Cross-sectional	MESA study	6814	48	45-84	CAC	• EAT volume was associated with the presence and severity of CAC, but these associations did not remain significant after adjustment for BMI • No significant interaction was found with gender or race/ethnicity	Age, square age, gender, race/ethnicity, smoking, physical activity, alcohol, education + BMI	14 (out of 16)
Bos, D. et al., The Netheraln ds, 2015[33]	Cross-sectional	Rotterdam study	2298	52	69±6.6	CAC	• EAT volume was independently associated with coronary calcification in men, but not in women.	Age, waist circumference, systolic blood pressure, diastolic blood ressure, use of blood pressure-lowering medication. Serum total cholesterol, serum HDL cholesterol, use of lipid-lowering medication, diabetes, and smoking status	14 (out of 16)
ii) Prospective outcomes									

Mahabadi A.A. et al., Germany, 2013[32]	Prospective Cohort	Heinz Nixdorf Recall Study	4093	47	59±8	MACE	• During the median follow-up of 8±1.5 yrs, doubling EAT volume was associated with more than 2-fold increase of risk of coronary events beyond traditional cardiovascular risk factors • After further adjustment for CAC, EAT volume remained a significant predictor of MACE	Age, gender, WC, systolic and diastolic blood pressure, antihypertensive medication, LDL-C, HDL-C, lipid-lowering medication, diabetes, smoking	16 (out of 16)
Mahabadi A. A. et al., Germany, 2014[31]	Prospective Cohort	Heinz Nixdorf Recall Study	3367	47	59±8	CAC progression	• EAT volume was higher in subjects with CAC progression, and this association was independent of traditional cardiovascular risk factors in young, non-obese and low CAC-subjects	Age, gender, BMI, systolic blood pressure, antihypertensive medication, LDL-C, HDL-C, lipid-lowering medication, triglycerides, diabetes, smoking status	16 (out of 16)
B. Hospital-based Studies									
Versteylen M. O. et al., 2012, Netherland[34]	Cross-sectional	Intermediate-risk of CAD	410	49	57±11.0	Moderate and severe coronary stenosis	• Diabetic patients had higher EAT volume than non-diabetic individuals independently of BMI • In crude analysis, EAT volume was associated with the presence and extent of CAD in diabetic and non-diabetic patients, but these associations did not remain significant following adjustment for confounders	Age, gender, systolic blood pressure, smoking	18 (out of 24)
Hell, M. et al., US, 2016[35]	Cross-sectional	Subjects with and without ischemia from the EISNER Registry	213 Ischaemia: 71 C: 142	90	60±9.9	Myocardial ischaemia	• Patients with myocardial ischaemia had higher volumes of EAT, and EAT increased the diagnostic accuracy of CT above CAC score	Age, gender, presence of symptoms and traditional cardiovascular risk factors	10 (out of 16)
Bettencourt, N. et al., 2012, Portugal[36]	Cross-sectional	Intermediate-risk of CAD	215	61	58±11.0	Coronary calcification	• EAT volume was correlated with coronary calcification independently of abdominal VAT • EAT was associated with an additional increase of 8% in men when compared women.	Age, gender, BMI, visceral abdominal fat, hypertension, dyslipidemia, diabetes mellitus, smoking	18 (out of 24)
Ito, T. et al., 2013, Japan[37]	Cross-sectional	Very low-risk patients with CAC equal zero	1308	46	59±12.3	Non-calcified coronary plaques	• EAT volume was higher in patients with obstructive non-calcified plaques (adj-OR, 95% CI: 1.10, 1.04-1.16) or vulnerable plaques (adj-OR, 95% CI: 1.19, 1.12-1.27)	Age, gender, hypertension, diabetes, typical symptoms	12 (out of 16)

							• EAT volume increased the diagnostic accuracy of Framingham Risk Score for the detection of obstructive non-calcified vulnerable plaques		
Tanami, Y. et al., US, 2015[38]	Cross-sectional	Intermediate to high-risk patients referred to CTA from the CORE320 Study	380	66	62*	Coronary stenosis, CAC, myocardial ischaemia	• There was a significant association between EAT volume and CAC in crude analysis, which did not remain significant in adjusted models • EAT volume was not associated with the presence of coronary stenosis or myocardial ischaemia	Age, gender, race, BMI, hypertension, dyslipidemia, family history of CAD, previous MI, diabetes, smoking status	10 (out of 16)

BMI: body mass index, CABG: coronary artery bypass grafting, CAC: coronary artery calcification, CAD: coronary artery disease, CI: confidence interval, CHD: coronary heart disease, CT: computed tomography, CTA: computed tomography angiography, EAT: epicardial adipose tissue, M: men, MACE: major adverse cardiovascular events, MI: myocardial infarction, SMART study: Secondary Manifestations of ARTerial disease cohort study, VAF: visceral abdominal fat, W: women, WC: waits circumference. *median. Methodological quality of all studies was assessed using the revised and validated version of the Methodological Index for Non-Randomized Studies (MINORS).

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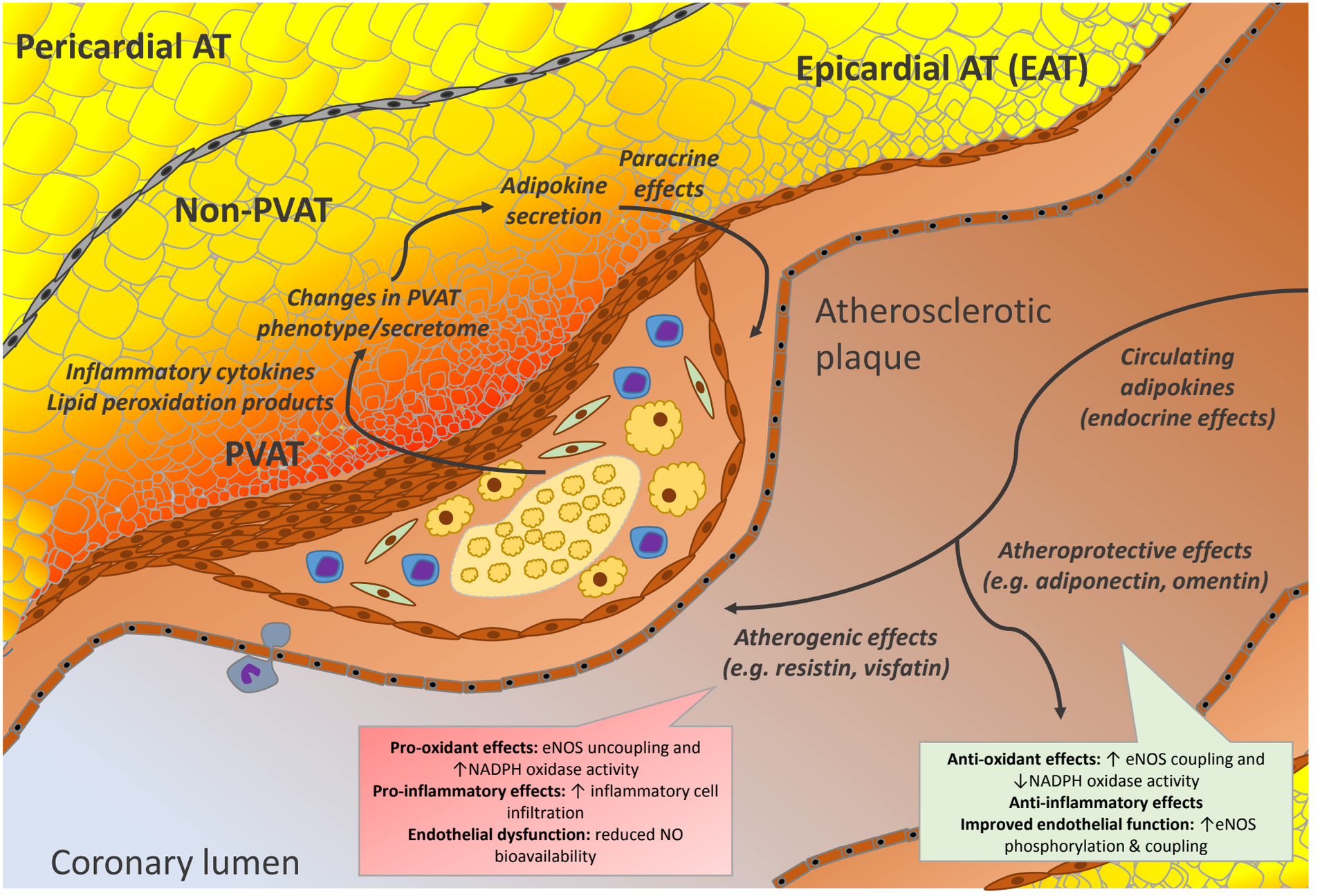
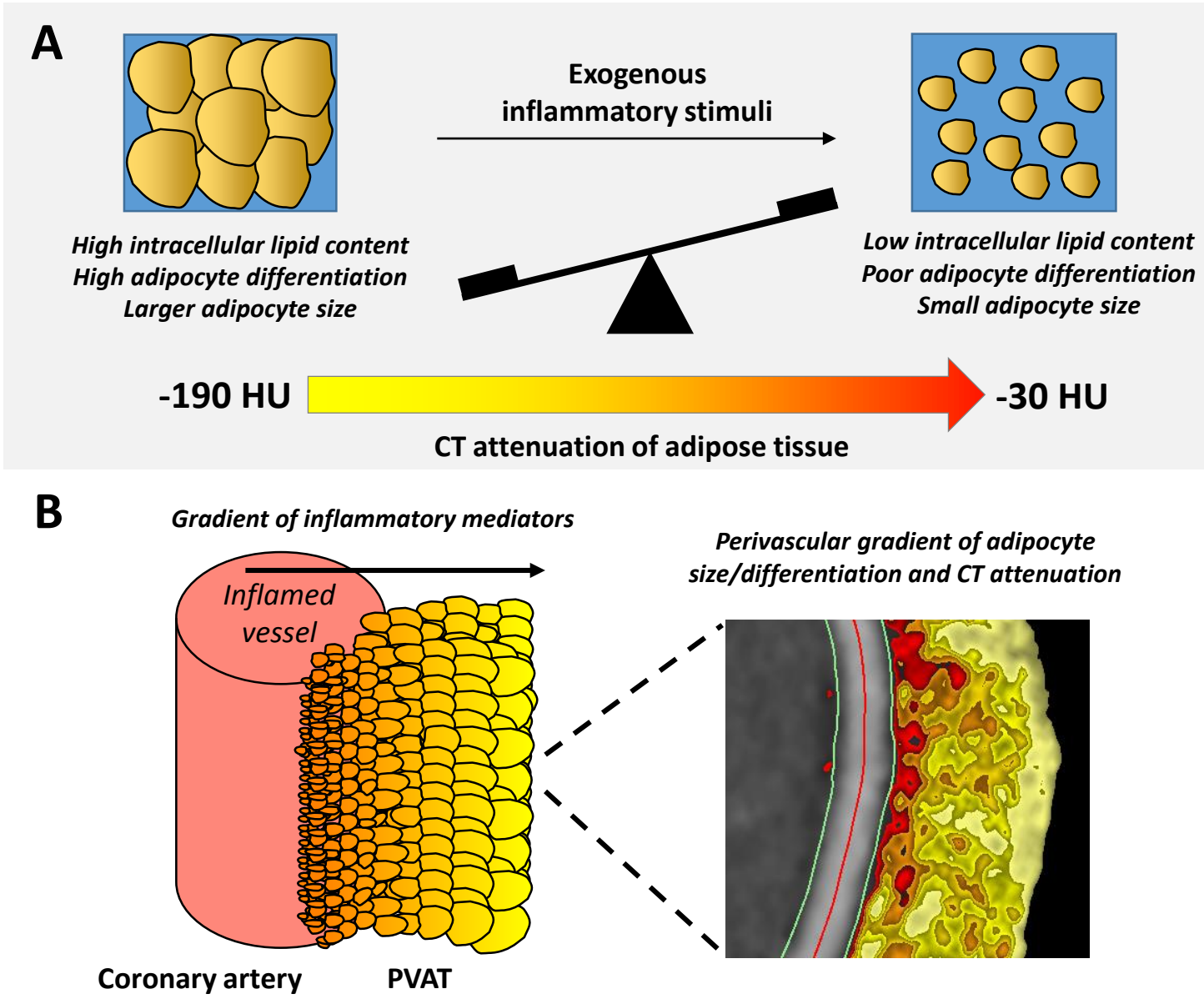
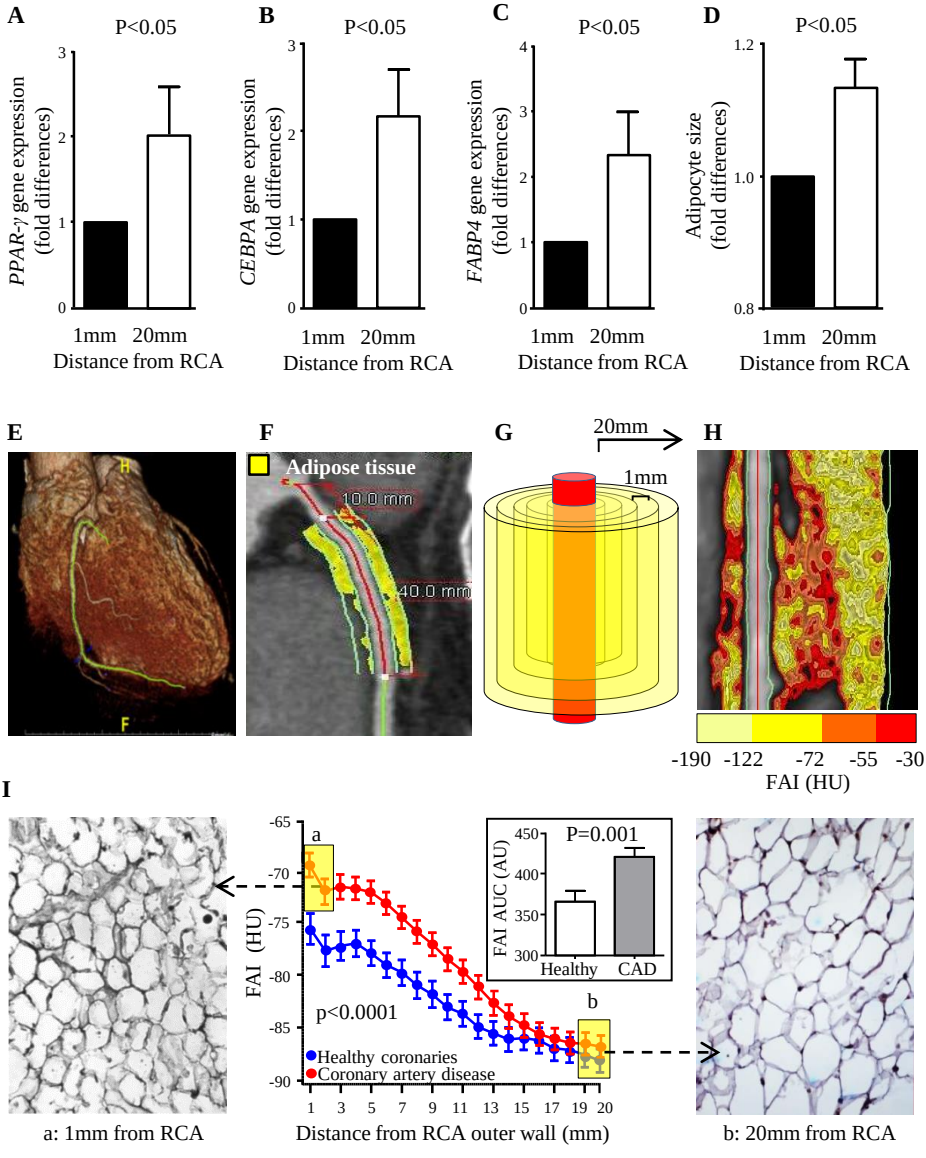

Pericardial AT
Epicardial AT (EAT)
Non-PVAT
Adipokine secretion
Paracrine effects
Changes in PVAT phenotype/secretome
Inflammatory cytokines
Lipid peroxidation products
PVAT
Atherosclerotic plaque
Circulating adipokines (endocrine effects)
Atheroprotective effects (e.g. adiponectin, omentin)
Atherogenic effects (e.g. resistin, visfatin)
Pro-oxidant effects: eNOS uncoupling and ↑NADPH oxidase activity
Pro-inflammatory effects: ↑ inflammatory cell infiltration
Endothelial dysfunction: reduced NO bioavailability
Anti-oxidant effects: ↑ eNOS coupling and ↓NADPH oxidase activity
Anti-inflammatory effects
Improved endothelial function: ↑eNOS phosphorylation & coupling
Coronary lumen
:Leukocytes
: Smooth muscle cells
: Endothelial cells
: Foam cells
: Adipocytes


A
Exogenous
inflammatory stimuli
High intracellular lipid content
High adipocyte differentiation
Larger adipocyte size
Low intracellular lipid content
Poor adipocyte differentiation
Small adipocyte size
-190 HU
-30 HU
CT attenuation of adipose tissue
B
Gradient of inflammatory mediators
Perivascular gradient of adipocyte
size/differentiation and CT attenuation
Inflamed
vessel
Coronary artery
PVAT


A
P<0.05
PPAR-γ gene expression (fold differences)
1mm 20mm
Distance from RCA
B
P<0.05
CEBPA gene expression (fold differences)
1mm 20mm
Distance from RCA
C
P<0.05
FABP4 gene expression (fold differences)
1mm 20mm
Distance from RCA
D
P<0.05
Adipocyte size (fold differences)
1mm 20mm
Distance from RCA
E
F
Adipose tissue
10.0 mm
40.0 mm
G
20mm
1mm
H
-190 -122 -72 -55 -30
FAI (HU)
I
a
b
FAI (HU)
p<0.0001
Healthy coronaries
Coronary artery disease
P=0.001
FAI AUC (AU)
Healthy
CAD
Distance from RCA outer wall (mm)
a: 1mm from RCA
b: 20mm from RCA