



Epicardial adipose tissue and cardiovascular disease: biology, imaging biomarkers, and therapeutic opportunities

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Keywords:

Epicardial adipose tissue, coronary artery disease, arrhythmias, heart failure, artificial intelligence

Citation: Zhang J, An Z, Luo H, Liu L, Zhang H, Zhang Y, Zhao X, Yang X, Zhang L, Tian J, Song X. Epicardial adipose tissue and cardiovascular disease: biology, imaging biomarkers, and therapeutic opportunities. *J Cardiovasc Aging*. 2026;6:33. <https://dx.doi.org/10.20517/jca.2025.60>

Received: 21 Nov 2025

First Decision: 23 Jan 2026

Revised: 8 Mar 2026

Accepted: 10 Jun 2026

Published: 24 Aug 2026

Academic Editor:

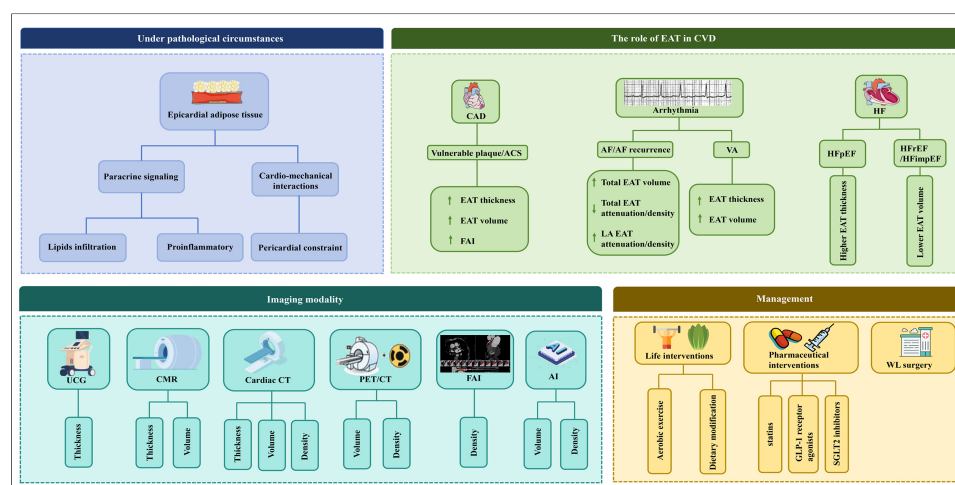
Joshua Hare

Copy Editor:

Ping Zhang

Production Editor:

Ping Zhang



Abstract

Cardiovascular diseases (CVDs) are characterized by high morbidity and mortality rates. Recent studies highlight the significance of epicardial adipose tissue (EAT) in the pathophysiology of coronary artery disease (CAD), arrhythmias, and heart failure (HF), primarily through its direct effects on cardiac structure and function mediated by inflammatory, metabolic, and biomechanical pathways. This review provides a comprehensive overview of the biology and regional variability of EAT, summarizes the molecular mechanisms linking EAT to obesity, aging, and the cardiovascular system, and discusses its potential clinical applications. EAT represents a promising imaging biomarker for CVD, with quantitative features, such as thickness, volume, and density, offering significant value for cardiovascular risk stratification. EAT-targeted therapies hold significant potential for the prevention and management of CVD. Furthermore, this review aims to inspire future research on the development of novel therapeutic strategies for

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cardiovascular conditions.

INTRODUCTION

Aging is characterized by declining biological function and increased vulnerability, with chronic low-grade inflammation, known as “inflammaging”, being a typical feature. This inflammatory state contributes to progressive tissue damage and degeneration. By promoting insulin resistance and increasing the risk of atherosclerosis, inflammaging increases the risk of cardiovascular disease (CVD) in older adults^[1]. CVD remains the leading cause of mortality worldwide, imposing significant social, economic, and public health burdens^[2]. In 2021, global estimates indicated that CVD affected approximately 612 million individuals and accounted for 26.8% of all deaths worldwide^[3]. Between 2020 and 2021, the United States experienced an estimated average annual cost of \$417.9 billion for CVD, including both direct and indirect expenses, with direct expenditures rising from \$189.7 billion in 2012-2013 to \$233.3 billion in 2020-2021^[4]. Furthermore, the age-standardized CVD mortality rate in East Asia exhibited considerable variation across countries and territories in 2021^[5].

Metabolic syndrome (MetS) is a well-established risk factor for CVD^[6]. In a multicenter study by Mongraw-Chaffin *et al.*^[7], 6,809 participants were enrolled in the Multi-Ethnic Study of Atherosclerosis to examine the combined effects of obesity and MetS on CVD and mortality. The findings demonstrated that MetS significantly mediated the relationship between obesity and CVD, highlighting a notable dose-response relationship between MetS duration and CVD incidence. Furthermore, the increasing prevalence of MetS is largely attributed to rising obesity rates^[6], which is recognized as a global pandemic and is generally defined as a body mass index (BMI) ≥ 30 kg/m²^[8,9]. In obesity, elevated visceral adipose tissue (VAT) deposition is closely associated with increased cardiometabolic risk and plays a crucial role in the development of CVD^[10,11]. Among individuals with severe obesity (BMI ≥ 35 kg/m²) without suspected or known cardiac disease, increased epicardial adipose tissue (EAT) thickness (> 5.4 mm) is independently associated with cardiac dysfunction^[8]. Additionally, a study examining the relationship between EAT and adverse outcomes, such as death or myocardial infarction (MI), has shown that although patients with elevated BMI generally exhibit a higher EAT volume (EATv), nearly one-third of those with elevated EATv have a BMI less than 30 kg/m². This finding suggests that EAT may provide incremental value beyond BMI in cardiovascular risk assessment^[12]. West *et al.*^[13] reported that a higher EATv (≥ 169.9 cm³ vs. < 169.9 cm³) is associated with an increased prospective risk of fatal and non-fatal MI, fatal and non-fatal stroke, non-cardiac mortality, and all-cause mortality. Given its strong prognostic value for all-cause mortality and major adverse cardiovascular events (MACE), EATv may serve as an important indicator of metabolically unhealthy visceral obesity.

Aging is marked by chronic low-grade inflammation and impaired adipose tissue (AT) function, similar to patterns observed in obesity. It promotes oxidative stress and inflammation in perivascular adipose tissue (PVAT) and is closely associated with cardiometabolic disorders^[14,15]. Additionally, aging significantly affects the properties of EAT and brown adipose tissue (BAT), facilitating a transition toward white adipose tissue (WAT)-like characteristics. This transition has important clinical implications, as it confers pro-inflammatory properties to EAT^[14,16,17]. Furthermore, a bidirectional relationship may exist between aging and EAT. Age-related changes in AT, including abnormal redistribution, a reduced progenitor pool, accumulation of senescent cells, and inflammatory activation, may further accelerate the aging process within the local microenvironment^[18].

The physiology, pathophysiology, and clinical implications of EAT have emerged as a rapidly advancing and highly productive area of research. This multidisciplinary field is highly relevant to contemporary cardiology

research and clinical practice^[19]. The recognized limitations of traditional anthropometric indices, such as BMI, in elucidating the correlation between obesity and CVD have prompted the adoption of advanced imaging modalities^[20], including echocardiography, cardiac computed tomography (CCT), cardiac magnetic resonance (CMR), and positron emission tomography (PET). Each imaging technique offers specific advantages and limitations. Quantitative features of EAT, such as volume and density, are important predictors of MACE^[12,21]. Furthermore, radiomics combined with artificial intelligence (AI), plays a crucial role in enabling automated EAT segmentation and quantification. This review presents a comprehensive and up-to-date overview of EAT's role in various physiological conditions and major CVDs, including coronary artery disease (CAD), arrhythmias, and heart failure (HF), and highlights the significance of quantitative assessment techniques and EAT-targeted therapies.

PATHOPHYSIOLOGY OF EAT

Classification and Definition of AT

AT is broadly classified into subcutaneous adipose tissue (SAT) and internal AT^[22]. SAT accounts for approximately 85% of total body fat and serves as the primary fat depot in the body^[23]. SAT expansion occurs through both adipocyte hypertrophy and hyperplasia, with the predominant mechanism varying by sex^[22,23]. Internal AT comprises intrathoracic and intra-abdominopelvic fat depots, such as omental and mesenteric AT^[22,24]. Cardiac AT is further categorized into EAT and pericardial adipose tissue (PAT) based on anatomical location. EAT is located between the myocardium and the visceral pericardium, whereas PAT resides on the outer surface of the parietal pericardium. According to its anatomical distribution, EAT can be further classified into peri-coronary EAT (directly surrounding or lying on the coronary artery adventitia), myocardial EAT (covering the myocardium), and periatrinal and periventricular EAT (distributed within and around the atria and ventricles, respectively)^[19,25,26].

EAT is a distinctive visceral fat depot and a marker of ectopic fat accumulation, exhibiting heterogeneous distribution throughout the heart^[11,19]. Its distribution is non-random, primarily corresponding to areas that require metabolic and structural support, particularly within the atrioventricular (AV) and interventricular sulci^[27,28]. Originating from the visceral pleural mesoderm, EAT has a complex histological composition that includes adipocytes, vascular and neural networks, and a high density of immune cells, such as macrophages, mast cells, and lymphocytes (e.g., T and B cells)^[27,28]. It contains both white adipocytes, which are responsible for energy storage, and brown adipocytes, which generate heat, thereby contributing to a beige AT phenotype^[29]. These cellular components interact to create a dynamic microenvironment in which metabolic and inflammatory signals converge^[28]. Functionally, EAT provides mechanical protection against shock and cardiac contractions^[29].

Current research on the effects of PAT on myocardial function is limited^[30,31], and the definition of PAT is not applied consistently. For example, some studies use the term “pericardial fat” to collectively refer to epicardial and paracardial fat^[30-32]. However, anatomically, PAT specifically refers to fat deposits attached to the parietal pericardium^[33,34]. Moreover, PAT and EAT differ in terms of embryology. Unlike EAT, PAT originates from the primitive thoracic mesenchyme and is supplied by non-coronary arteries^[35].

Healthy EAT

Under physiological conditions, EAT is essential for maintaining cardiac function and metabolic homeostasis^[11,19]. Specifically, EAT supports myocardial energy requirements by absorbing and releasing free fatty acids (FFAs), the oxidation of which accounts for approximately 50%-70% of cardiac energy production^[36]. Functionally, EAT acts as a local fatty acid buffer, limiting excessive FFA exposure to the myocardium and potentially providing mechanical protection^[23,29]. Histologically, EAT is generally classified as WAT, characterized by unilocular adipocytes. However, brown multilocular adipocyte niches have also

been identified near the epicardial surface^[37]. These BAT-like adipocytes are rich in mitochondria and are capable of expressing uncoupling protein 1 (UCP1)^[23,37-39]. During fetal and early neonatal life, EAT exhibits BAT-like properties. The BAT-like thermogenic profile of EAT during this period is thought to protect the immature myocardium from thermal stress and to provide a local energy reservoir for metabolically active cardiac tissue^[37]. With aging, EAT may transition from brown-like to white-like phenotypes^[36,37], marked by progressive loss of UCP1 expression, diminished thermogenic gene features, and reduced mitochondrial density^[23,37,40]. EAT expresses CD137, a marker of beige AT, supporting the notion that EAT can transition between brown-like and white-like phenotypes^[37]. Browning of the EAT may occur in response to physiological stimuli, including cold exposure, diet, and exercise^[23,40,41]. Beige adipocytes develop within WAT through the browning process, whereas classical brown adipocytes are primarily distributed in dedicated BAT depots, such as the interscapular and supraclavicular regions^[37,39,41]. Beige and white adipocytes originate from mesodermal mesenchymal stem cells (MSCs), whereas classical BAT primarily derives from dermomyotomes^[37,39,41]. Similar to BAT, beige AT is rich in mitochondria and highly expresses UCP1.

EAT secretes both protective adipokines, such as adiponectin and omentin, and pro-inflammatory mediators, including leptin. Macrophages, the predominant immune cells in EAT, further contribute to local inflammation by releasing cytokines, such as tumor necrosis factor- α (TNF- α) and interleukin-6 (IL-6)^[27,28,42]. Notably, EAT is also enriched in genes encoding cardioprotective adipokines, including adiponectin^[23], an endogenous insulin sensitizer that reduces insulin resistance by enhancing fatty acid (FA) oxidation and promoting glucose utilization in the skeletal muscle and liver^[43].

Previous research has shown that adiponectin enhances AT's capacity to function as an efficient metabolic sink. Bauzá-Thorbrügge *et al.*^[39] established adiponectin-overexpressing transgenic mice to examine the effects of adiponectin on AT expansion and mitochondrial function in adipocytes. Their findings demonstrated that elevated adiponectin levels promoted the expansion and differentiation of Lineage - Sca1+CD34- "beige-like" adipocyte precursor cells (APCs) in both BAT and inguinal WAT (iWAT). This process was associated with enhanced browning and metabolic activity in iWAT, whereas BAT exhibited a whiter, less thermogenically active phenotype. The authors suggested that adiponectin modulates adipocyte metabolic activity by enhancing sympathetic innervation within the AT and maintaining mitochondrial function in adipocytes. Additionally, adiponectin exhibits anti-inflammatory properties; in monocytes and macrophages, it suppresses TNF- α and IL-6 production, while inducing IL-10 and IL-1 receptor antagonists. It also reduces the production of interferon-gamma (IFN- γ) and IL-17 by T lymphocytes^[43].

Under physiological conditions, leptin plays a crucial role in regulating food intake and energy metabolism. However, its cardioprotective or detrimental effects are determined by factors such as the microenvironment, leptin concentration, and duration of exposure^[44].

Pathological EAT

Under pathological conditions, EAT can exert direct harmful effects on cardiomyocytes, primarily because of its proximity to the heart. EAT lacks clearly defined boundaries and shares unobstructed microcirculation with adjacent myocardial tissue, facilitating the local transfer of hormonal factors and bioactive molecules^[45,46]. However, EAT may also demonstrate protective effects in specific disease states, highlighting its dual role in cardiac functions.

VAT accumulation may result from SAT dysfunction. When SAT reaches its maximal expansion capacity and loses its energy buffering function, lipids are increasingly redirected to VAT and other ectopic fat deposition sites, such as the heart, liver, kidneys, and pancreas^[22,23,47]. Ectopic fat deposition around the heart can significantly impair cardiovascular function, particularly in individuals with visceral obesity^[11,23].

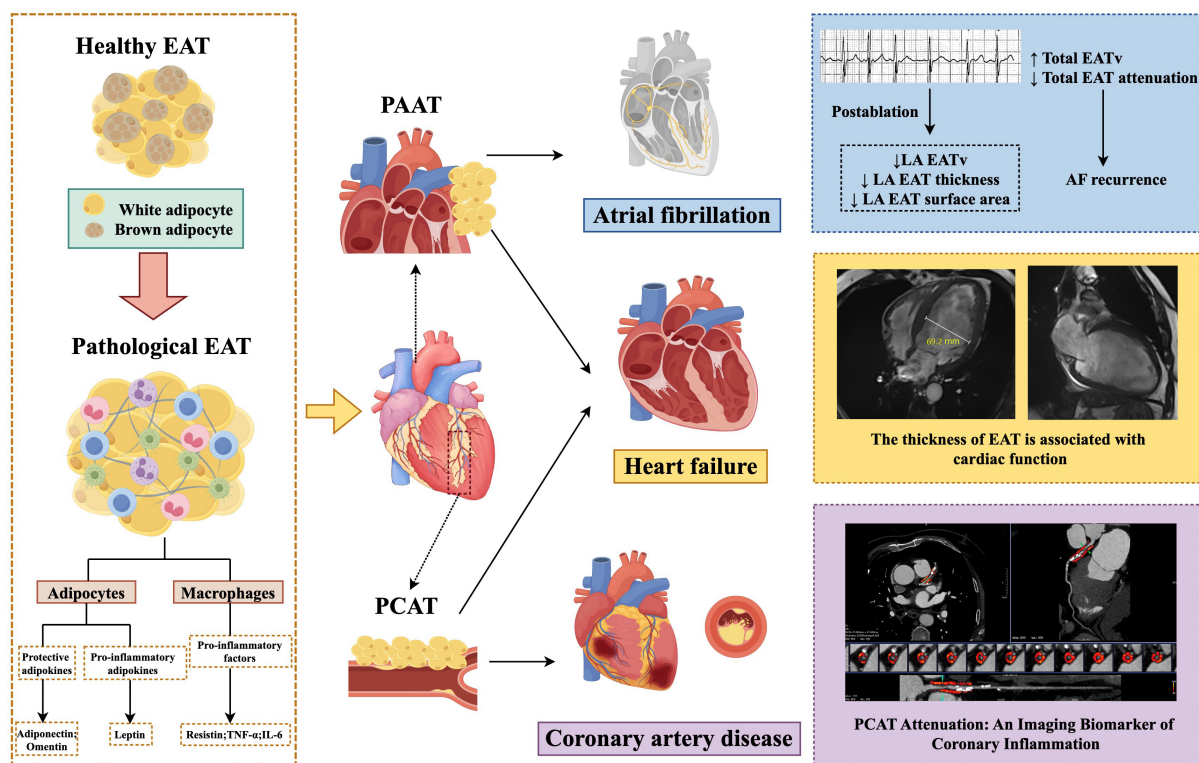


Figure 1. Regional distribution of EAT and its differential impact on CVD. Under pathological conditions, EAT undergoes a phenotypic transition from a protective phenotype to an inflammatory substrate, becoming a source of pro-inflammatory, pro-atherogenic, and pro-arrhythmogenic mediators (bottom-left). Following AF ablation, LA EATv decreases. Patients experiencing AF recurrence exhibit higher pre-ablation total EATv, lower EAT attenuation values, and progressive EATv enlargement during follow-up (top-right). EAT thickness is associated with cardiac function (middle-right). Elevated PCAT attenuation/density correlates with CAD. Compared to patients with stable CAD, those with ACS exhibit a stronger inflammatory response around coronary lesions (bottom-right). The top-right, middle-right and bottom-right panels show patients from Beijing Anzhen Hospital, Capital Medical University, Beijing, China. Patient consent was obtained for the use of this image, and all personally identifiable information has been removed. The image was created on the website FigDraw.com (ID: OTUPWf87ff). ACS: Acute coronary syndrome; AF: atrial fibrillation; CAD: coronary artery disease; CCTA: coronary computed tomography angiography; CVD: cardiovascular disease; EAT: epicardial adipose tissue; IL-6: interleukin-6; PCAT: peri-coronary adipose tissue; TNF- α : tumor necrosis factor- α ; LA: left atrium; EATv: epicardial adipose tissue volume; PAAT: periatrial adipose tissue.

Long-term pathological FA oversupply may exceed myocardial β -oxidation capacity, leading to increased intracellular lipid storage and the accumulation of lipotoxic intermediates^[11], which subsequently compromises cardiac function.

Accumulating evidence indicates that obesity contributes to CVD by promoting pathological remodeling of AT, characterized by adipocyte hyperplasia and hypertrophy, chronic low-grade inflammation, immune cell infiltration, and an imbalanced adipokine profile. This imbalance alters the AT microenvironment, particularly by enhancing immune cell infiltration, ultimately triggering chronic, low-grade systemic inflammation, referred to as “metaflammation”^[42,43,48,49]. Furthermore, during aging or in the presence of chronic cardiometabolic diseases, EAT undergoes phenotypic switching, gradually losing its BAT-like characteristics^[36]. This phenotypic transition converts EAT from a protective depot into a pro-inflammatory substrate^[50].

Pathological remodeling of EAT is characterized by altered adipokine signaling, macrophage activation, and progressive fibrotic changes, resulting in a pro-inflammatory and pro-fibrotic microenvironment. Owing to its direct anatomical proximity to the myocardium and coronary arteries, excessive and dysfunctional EAT can promote arrhythmias, cardiac structural remodeling, and atherosclerotic disease development through paracrine and vasocrine signaling, as well as cardio-mechanical interactions^[36,51,52] [Figure 1].

Obesity is characterized by elevated circulating leptin levels that are proportional to increased AT mass; however, individuals with obesity commonly develop leptin resistance^[43,53]. Chen *et al.*^[44] developed a rat model of MetS by administering a high-fat diet for 12 weeks. EAT was isolated from each group, and EAT-conditioned medium was used to treat H9C2 rat cardiomyoblasts *in vitro*. The results demonstrated that MetS rats displayed abnormal myocardial structure and impaired diastolic function, with preserved systolic function, particularly in the subepicardial region. The severity of the myocardial injury correlated with EAT-derived leptin levels rather than serum leptin levels, indicating that EAT-derived leptin may be a key mediator of MetS-related myocardial injury. Mechanistically, EAT-derived leptin induces MetS-related myocardial injury via two cooperative pathways involving the protein kinase C/nicotinamide adenine dinucleotide phosphate (NADPH) oxidase/reactive oxygen species (ROS) pathway: first, by promoting mitochondrial oxidative stress and dysfunction, leading to mitochondrial pathway apoptosis; and second, by stimulating activator protein-1 (AP-1) nuclear translocation, which promotes inflammatory activation.

Elevated concentrations of pro-inflammatory mediators in EAT, such as IL-6, TNF- α , and monocyte chemoattractant protein-1 (MCP-1), are implicated in the increased retention of inflammatory cells. The infiltration of specific inflammatory cells, including macrophages (CD68⁺), T lymphocytes (CD3⁺), and mast cells (tryptase⁺), has been documented in EAT^[54]. A growing body of research has examined adipose tissue macrophages (ATMs) and their phenotypes. Macrophages are traditionally classified as either classically activated (M1), induced by pro-inflammatory mediators such as lipopolysaccharide (LPS) and IFN- γ , or alternatively activated (M2), generated following *in vitro* exposure to IL-4 and IL-13^[55,56]. However, Kratz *et al.*^[57] reported that exposure of macrophages to glucose, insulin, and palmitate, conditions that mimic MetS, produces a distinct “metabolic activation (MMe)” macrophage phenotype. This phenotype differs mechanistically from classical activation and is driven by pathways specific to metabolic disease. In obesity-associated insulin resistance, ATMs are chronically exposed to an environment rich in excess FFAs, particularly saturated FFAs such as palmitate. Palmitate promotes pro-inflammatory cytokine production by binding to cell-surface Toll-like receptors (TLRs), while its internalization activates p62/peroxisome proliferator-activated receptor gamma (PPAR γ) pathways, enhancing lipid metabolism and limiting inflammatory responses. The balance between these two relatively independent mechanisms determines the overall macrophage response to metabolic dysfunction, resulting in complex phenotypes spanning the spectrum from M1-like and M2-like states. Building upon the concept of metabolic activation, Boutens *et al.*^[58] reported that ATMs in obese mice exhibit unique metabolic characteristics, including simultaneous upregulation of glycolysis and oxidative phosphorylation (OXPHOS), distinguishing them from the metabolic profiles of either M1 or M2 macrophages. Glycolysis appears to be a primary driver of inflammatory cytokine release in obese ATMs, as inhibition of glycolysis with 2-deoxy-D-glucose (2-DG) eliminated the basal differences in cytokine release between ATMs from obese and lean mice. Although hypoxia-inducible factor-1 α (HIF-1 α), a key regulator of glycolysis, was upregulated in obese ATMs, myeloid-specific deletion of HIF-1 α did not alter the inflammatory status of AT in obese mice. These findings indicate that HIF-1 α is not essential for the proinflammatory activation of ATMs during the early stages of obesity. Collectively, these studies suggest that obese ATMs cannot be fully characterized by the traditional M1/M2 classification; rather, they represent disease-specific functional states shaped by local microenvironmental cues, metabolic programs, and activated signaling pathways.

Excessive accumulation of EAT exerts mechanical pressure that disrupts the local hemodynamic environment in adjacent coronary arteries. This disruption can contribute to coronary artery narrowing and reduced blood flow, increasing the risk of localized ischemia and accelerating atherosclerosis development^[59,60]. Consequently, the maladaptive accumulation and altered biology of EAT can also affect the adjacent coronary arteries, atrial myocardium, and ventricular myocardium. These changes may promote coronary plaque instability and increase atrial and ventricular fibrosis, thereby impairing the myocardial

electrophysiological properties and distensibility^[46].

Emerging evidence suggests that AT may exert protective effects during pathological conditions. Sárvári *et al.*^[61] demonstrated that, during the phagocytosis of adipocyte-derived fragments, IL-6 was secreted independently, without concurrent induction of TNF- α and IL-1 β , which differs from the classical activation pattern of the nuclear factor κ B (NF- κ B) inflammatory pathway. These findings suggest that IL-6 may serve a regulatory function in obesity-associated AT inflammation, rather than acting solely as a pro-inflammatory cytokine. This regulatory mechanism may help maintain AT homeostasis and provide protection against MetS-related pathologies, such as insulin resistance. Additionally, recent studies have reported that central leptin signaling improves cardiac function following myocardial ischemia-reperfusion (IR) injury^[62]. Specifically, central leptin infusion for 28 days post-IR injury increased the release of extracellular vesicles (EVs) derived from BAT and enhanced myocardial contractility. Mechanistically, activation of brain leptin receptors elevates sympathetic activity to the BAT, thereby stimulating the release of EVs enriched in microRNA-29c-3p. These EVs suppress cardiac fibrosis and improve overall cardiac function by regulating mitochondrial activity and reducing collagen deposition^[62]. EAT-derived EVs are regarded as key mediators linking EAT to the pathogenesis of CVD due to their ability to transport bioactive molecules^[26]. EVs, including those from EAT, are known to participate in various CVD-related pathological processes by carrying multiple microRNAs (miRNAs). For example, EVs isolated from diabetic adipocytes or from nondiabetic adipocytes exposed to high-glucose or high-lipid conditions, which are enriched in miR-130b-3p, exacerbate IR injury in diabetic hearts. miR-3064-5p is highly expressed in EAT-derived EVs from patients with coronary atherosclerotic heart disease and may contribute to CAD pathogenesis by disrupting normal adipocyte maturation of EAT stem cells. Additionally, hypertrophic adipocyte-derived EVs enriched in miR-802-5p induce insulin resistance in neonatal rat ventricular myocytes by suppressing protein kinase B (AKT) phosphorylation and glucose uptake, indicating a potential role in diabetic cardiomyopathy-related HF. EAT-derived EVs from patients with atrial fibrillation (AF) exhibit increased levels of miR-1-3p and miR-133a-3p, which may promote arrhythmogenic remodeling by downregulating the expression of *Kcnj2* and *Kcnj12* genes^[26].

In summary, due to its unique anatomical location and pathophysiological properties, EAT may contribute to the development and progression of CVD through multiple mechanisms. Quantitative imaging parameters of EAT, such as thickness, volume, and density, are strongly associated with CVD and adverse cardiovascular events. Moreover, these imaging-derived indicators may facilitate the connection between structural and functional changes in EAT and clinical outcomes, thereby providing potential value for cardiovascular risk assessment and prognosis.

QUANTIFICATION AND CHARACTERIZATION OF EAT

The clinical assessment of EAT is essential for diagnosing and stratifying CVD risk. Recent advancements in imaging modalities have significantly improved the accuracy of EAT quantification. However, each imaging technique has specific strengths and limitations, as summarized in [Table 1].

Imaging and measurement of EAT in CVD

Echocardiography

Standard two-dimensional echocardiography is used to assess EAT thickness through parasternal long-axis and short-axis views. EAT is defined as a relatively echo-free space situated between the outer myocardial layer and the visceral pericardium, with measurements averaged over three consecutive cardiac cycles. Since EAT is compressed during diastole, its thickness is optimally assessed at end-systole on the right ventricular (RV) free wall, where the ultrasound beam is positioned perpendicular to the myocardium and the aortic

Table 1. Quantification and characterization of EAT

Imaging modality/parameter	Measurement	Advantages	Disadvantages	Reference
Echocardiography	Thickness	Low cost; safe; widely available; non-invasive	Low image quality in obese patients; inability to assess regional EAT distribution; limited reproducibility; no volumetric quantification	[19,63-67]
CMR	Thickness; volume	Safety; good reproducibility; allows regional EAT localization; can measure intramyocardial lipid content	High cost; limited accessibility; long scan time; prolonged breath-holding	[19,63,65-68]
CCT	Thickness; volume; density	High resolution; excellent reproducibility; relatively easy to operate; allows regional EAT localization	Ionizing radiation; contrast exposure; relatively high cost	[19,63,65-67]
PET/CT	Volume; inflammatory activity	Can assess EAT inflammatory activity; detects high-risk coronary plaques	Ionizing radiation; high cost; limited accessibility	[19,69-71]
FAI	Density/attenuation	High sensitivity and specificity in detecting coronary (perivascular) inflammation	Limited accessibility; high cost; requires further validation	[19,66,72-74]
AI	Volume; density	Automated quantification; high accuracy; excellent reproducibility; reduced annotation time	High cost; limited availability; lack of standardization; requires further validation	[12,13,19,75-80]

AI: Artificial intelligence; CCT: cardiac computed tomography; CMR: cardiac magnetic resonance; EAT: epicardial adipose tissue; FAI: fat attenuation index; PET: positron emission tomography; CT: computed tomography.

annulus serves as an anatomical landmark. EAT thickness ranges from 1 mm to 23 mm, and when it exceeds 15 mm, it may appear as a hyperechoic space on ultrasound images^[64]. Echocardiography offers several clinical advantages, including low cost, safety, wide availability, and non-invasiveness. However, its limitations include suboptimal image quality in obese individuals, inability to provide volumetric measurements, limited evaluation of regional EAT distribution, and challenges with reproducibility^[19,63-67].

CMR

CMR imaging enables assessment of atrial and ventricular volumes, predominantly ventricular myocardial fibrosis, and myocardial perfusion, which may help elucidate the mechanisms underlying AF pathogenesis^[67]. CMR is also utilized to obtain both thickness and volume measurements of EAT. Furthermore, it supports the evaluation of cardiac changes across multiple imaging sequences and allows quantitative measurement of total EATv and PVAT volume. Entropy, an emerging CMR-derived parameter, quantifies EAT homogeneity and distributional uncertainty from the full signal-intensity distribution. This parameter may indirectly reflect EAT heterogeneity, which is associated with spatial variations in structural, functional, and molecular characteristics^[81]. Notably, CMR uses magnetic fields and low-energy radiofrequency pulses instead of ionizing radiation for image acquisition, making it a radiation-free imaging modality^[68]. The advantages of CMR include safety, good reproducibility, the ability to localize regional EAT, and the capability to measure intramyocardial lipid content. However, limitations include prolonged scan time, high costs, limited accessibility, and the need for extended breath-holding^[19,63,65-67].

CCT

Despite exposure to ionizing radiation^[63], CCT remains the predominant imaging modality in clinical studies examining the association between EAT and CVD^[67]. CCT provides comprehensive measurements of EAT, including its thickness, volume, and density. Its advantages include high spatial resolution, excellent

reproducibility, relative ease of operation, and the ability to assess regional EAT localization, such as atrial EAT or peri-coronary adipose tissue (PCAT)^[19,63,65-67]. Compared with echocardiography, CCT offers superior spatial resolution and the ability to generate three-dimensional cardiac images. However, its limitations include radiation exposure, and in the case of coronary computed tomography angiography (CCTA), exposure to iodinated contrast agents^[19,63,65-67].

PET/CT

¹⁸F-fluorodeoxyglucose (¹⁸F-FDG) PET/CT enables assessment of EAT inflammatory activity, while its CT component quantifies EATv^[19,69]. ¹⁸F-Sodium Fluoride (¹⁸F-NaF) PET can be used to identify high-risk atherosclerotic lesions with active calcification. Kitagawa *et al.*^[70] demonstrated that increased perilesional EAT density on CT is associated with significant ¹⁸F-NaF coronary uptake. Specifically, perilesional fat density measured on non-contrast CT images, with a threshold ≥ -97 Hounsfield units (HU), predicts the presence of lesions with elevated ¹⁸F-NaF coronary uptake. Sequential integration of CT-derived EAT density and coronary arterial ¹⁸F-NaF uptake on PET may improve risk stratification in CAD. Furthermore, in stable patients with high-risk plaque features on CCTA, increased PCAT density was significantly associated with ¹⁸F-NaF coronary uptake. As ¹⁸F-NaF uptake indicates active coronary microcalcification and increased PCAT density is associated with vascular inflammation, their combined assessment may provide complementary insights into plaque activity and improve CAD risk stratification^[71]. However, these imaging techniques are limited by exposure to ionizing radiation, high cost, and limited availability^[19].

Fat attenuation index

On CCTA, AT is defined as voxels with attenuation values ranging from -190 to -30 HU, and its mean attenuation within a predefined volume of interest is quantified as the fat attenuation index (FAI)^[72]. As a novel imaging biomarker, FAI enables quantification of coronary artery inflammation by mapping spatial variations in PVAT attenuation on CCTA^[73,74]. Coronary inflammation inhibits lipid accumulation and adipocyte differentiation in the adjacent PVAT, establishing a radial gradient in adipocyte lipid content. Adipocytes near the vessel wall are typically smaller, less differentiated, and lipid-poor, resulting in higher FAI, consistent with increased local inflammation^[72-74]. FAI has demonstrated robust diagnostic performance in detecting coronary inflammation, as evaluated by ¹⁸F-FDG uptake on PET^[72]. However, the limitations of FAI include limited clinical availability, high cost, and the need for further research to evaluate its utility in assessing regional EAT activity^[19]. Collectively, FAI has emerged as a valuable diagnostic and prognostic marker of PCAT inflammation in CAD. Evidence suggests that elevated periatrial adipose tissue fat attenuation index (PAAT FAI) is associated with the occurrence of AF, its recurrence following catheter ablation, and AF persistence^[66,82,83]. In contrast, reduced total EAT FAI may be associated with AF recurrence^[66,84].

Metabolomic and lipidomic profiling of EAT

Metabolomics enables the identification of high-resolution, multifactorial phenotypic signatures of complex diseases by detecting small-molecule changes in biological samples. This approach provides insights into disease-related molecular pathways and holds promise for diagnosing disease, monitoring disease progression, and evaluating therapeutic responses^[85,86]. In the Multi-Ethnic Study of Atherosclerosis, the association between EAT metabolomic profiles and EATv was analyzed using untargeted ¹H nuclear magnetic resonance (¹H NMR)-based metabolomics, including one-dimensional NMR spectroscopy, Carr-Purcell-Meiboom-Gill (CPMG) analysis, and lipidomics, with subsequent validation in the Rotterdam Study. By evaluating 23,571 metabolomic spectral variables, Neeland *et al.*^[87] reported a positive correlation between serum metabolites and EAT, including 1,5-anhydrosorbitol (1,5-AG) and glycoproteins, whereas phospholipids demonstrated a negative correlation. Additionally, markers of atherogenic dyslipidemia were positively associated with EAT. The association between 1,5-AG, an indicator of short-term glycemic

metabolism, and EAT suggests that the pathophysiological effects of EAT may extend beyond the local cardiac environment and may be related to short-term glycemic fluctuations and systemic glucose regulation. In advanced HF, EAT undergoes metabolic remodeling, characterized by impaired FA oxidation and increased local production of L-3-hydroxybutyrate (L-3-HB) near the myocardium, highlighting the close metabolic cooperation in nutrient supply between EAT and the heart via the coronary circulation^[88].

Plasma lipidomics involves the analysis of overall lipid class concentrations, FA profiles, and individual lipid species^[89]. EAT exhibits a distinct lipidomic profile in CAD, characterized by significant elevations in proinflammatory lipids, such as ceramides and diacylglycerols (DAGs). Ceramides, as lipotoxic molecules, impair β -cell function and disrupt mitochondrial metabolism, ultimately resulting in cellular dysfunction and apoptosis^[90]. Furthermore, studies have demonstrated a positive correlation between lipoprotein lipase (LPL) activity and ceramide content in EAT, suggesting that LPL hydrolyzes triglycerides (TGs) derived from very low-density lipoproteins (VLDL) and chylomicrons to supply FFAs, potentially contributing to EAT expansion^[91].

AI-based EAT segmentation and quantification

Despite being established metrics for cardiovascular risk assessment, EAT volume and attenuation require approximately 15 min of manual annotation per case, which limits their use in routine clinical practice^[12]. AI-based methods offer potential solutions by enabling automated image segmentation and quantification. These methods include machine learning (ML), with deep learning (DL) as a more advanced subset of ML^[92]. In parallel, clinical CT image reconstruction has evolved from traditional filtered back projection and iterative reconstruction to DL-based algorithms, thereby improving image quality and potentially influencing quantitative measures such as PCAT and EAT attenuation^[93].

ML is increasingly integrated into clinical practice to analyze multiple quantitative variables and enhance the accuracy of prognostic predictions^[76]. Non-contrast CT calcium scoring (CTCS) provides direct evidence of coronary atherosclerosis by detecting coronary artery calcification (CAC). However, the CTCS's ability to predict high-risk plaque features remains insufficiently explored. Lee *et al.*^[77] developed CatBoost, an innovative ML model for predicting coronary arterial remodeling using EAT and calcification features derived from low- or no-cost screening CTCS scans. Their findings demonstrated that positive remodeling, defined as outward arterial expansion in response to atherosclerotic plaque accumulation, serves as a strong indicator of MACE risk. Furthermore, spatial distribution features of fat voxels in fat-omics exert the greatest influence on model predictions and may be relevant to MACE risk stratification^[78]. In addition to CAD, radiomic features derived from CTCS, such as calcium-omics and fat-omics, can also be used in HF risk models, outperforming traditional clinical factors^[79].

DL, particularly convolutional neural networks (CNNs), is widely utilized for automated image segmentation. Commandeur *et al.*^[75] developed a representative model that quantified EATv and density from CTCS using a DL-based system and further evaluated the clinical significance of automated EAT assessment. The volumetric progression of EAT was associated with the progression of high-risk non-calcified plaques. Additionally, a higher quantified EATv was associated with cardiovascular risk factors. For example, higher EATv was linked to hypertension (an increase of 18.02 cm³, $P < 0.001$) and diabetes (an increase of 18.33 cm³, $P < 0.001$). Furthermore, West *et al.*^[13] developed and validated a DL network for volumetric quantification of EAT using a large training dataset. Specifically, this network performs whole-heart pericardial segmentation in CCTA using a 3D residual U-Net architecture. The study implemented a feedback learning mechanism in which automated EAT segmentation results from the DL network were corrected by experts and subsequently used to optimize the network iteratively^[13,80]. Additionally, Miller *et al.*^[12] developed a DL-based model to automatically quantify EAT volume and attenuation from low-dose ungated CT acquired without cardiac-cycle synchronization, and evaluated the association of these measurements with death or MI. The model first identified the cardiac silhouette and then segmented EAT

using attenuation thresholds, reducing annotation time to < 2 s while demonstrating excellent agreement with expert annotations. Furthermore, elevated EAT volume and attenuation were independently associated with an increased risk of death or MI during follow-up.

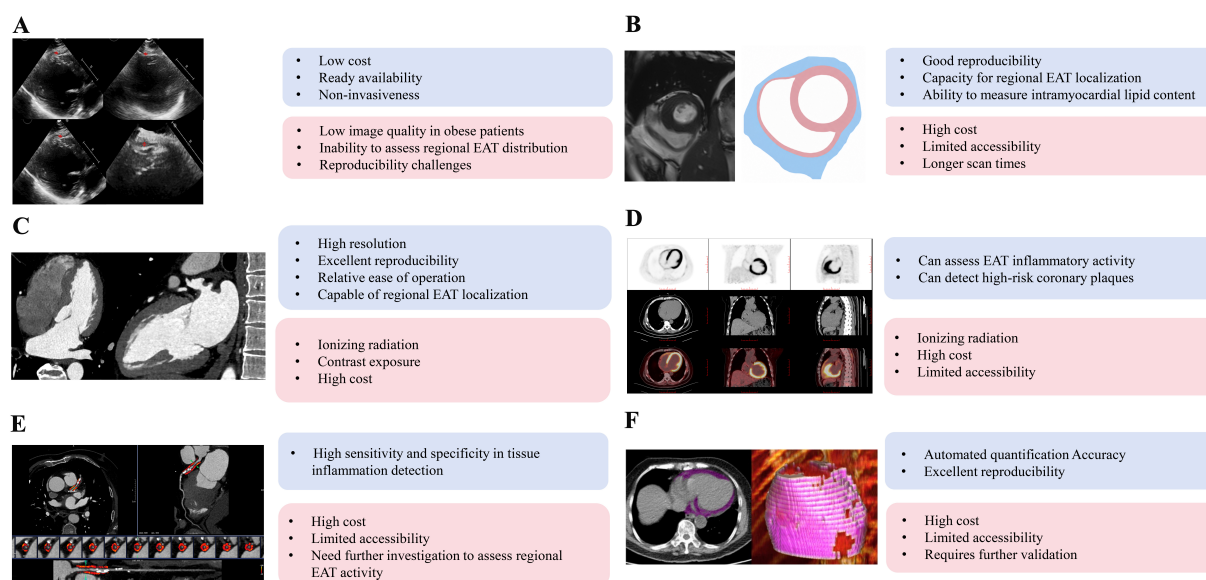


Figure 2. Quantification and characterization of EAT. (A) Echocardiography serves as a quantitative tool for measuring EAT thickness; (B) CMR can measure both EAT thickness and volume; (C) CCT is capable of measuring EAT thickness, volume, and density; (D) PET/CT quantitatively assesses EAT volume and inflammatory activity; (E) FAI reflects the intensity of coronary artery inflammation by measuring PCAT attenuation; (F) AI-based methods enable automated segmentation and quantification of EAT volume and attenuation/density. Blue boxes indicate advantages, and pink boxes indicate disadvantages. Figure 2A is adapted from Vianello et al.^[94], and Figure 2F is adapted from Miller et al.^[12]. Both Figure 2A and F are licensed under CC BY 4.0 (<https://creativecommons.org/licenses/by/4.0/>). Figure 2B-E show patients from Beijing Anzhen Hospital, Capital Medical University, Beijing, China. Patient consent was obtained for the use of this image, and all personally identifiable information has been removed. AI: Artificial intelligence; CCT: cardiac computed tomography; CMR: cardiac magnetic resonance; EAT: epicardial adipose tissue; FAI: fat attenuation index; PET: positron emission tomography; PCAT: peri-coronary adipose tissue; CT: computed tomography.

In summary, echocardiography, CMR, and CCT are viable modalities for assessing EAT, each presenting distinct advantages and limitations [Figure 2]. Echocardiography is convenient but primarily limited to measuring EAT thickness. CMR offers high tissue resolution, although it is very expensive and less accessible in routine clinical settings. In contrast, CCT offers greater flexibility in clinical applications, and its derived FAI enables quantitative assessment of spatial variations in PVAT attenuation that reflect tissue inflammation. Furthermore, CCTA can be integrated with AI to automate EAT segmentation and quantification, thereby enhancing its clinical utility. Based on these considerations, CCTA has been proposed as one of the most practical imaging modalities for EAT evaluation.

ROLE OF EAT IN CVD

EAT displays region-specific transcriptome profiles. Specifically, EAT is localized around the left atrium (LA) and infiltrates the coronary arteries. Both PCAT and LA EAT play significant roles in the pathogenesis of CAD, arrhythmias, and the progression of HF [Figure 1]^[19,95]. Figure 3 illustrates the relevant signaling pathways, and Table 2 summarizes the associated molecular mechanisms and EAT alterations associated with CAD, AF, and HF.

EAT in the development of CAD

EAT serves as an independent and significant predictor of severe and complex CAD, functioning both as a potential risk marker and therapeutic target [Figure 1 and Table 2]^[118]. Excessive FFAs released from EAT

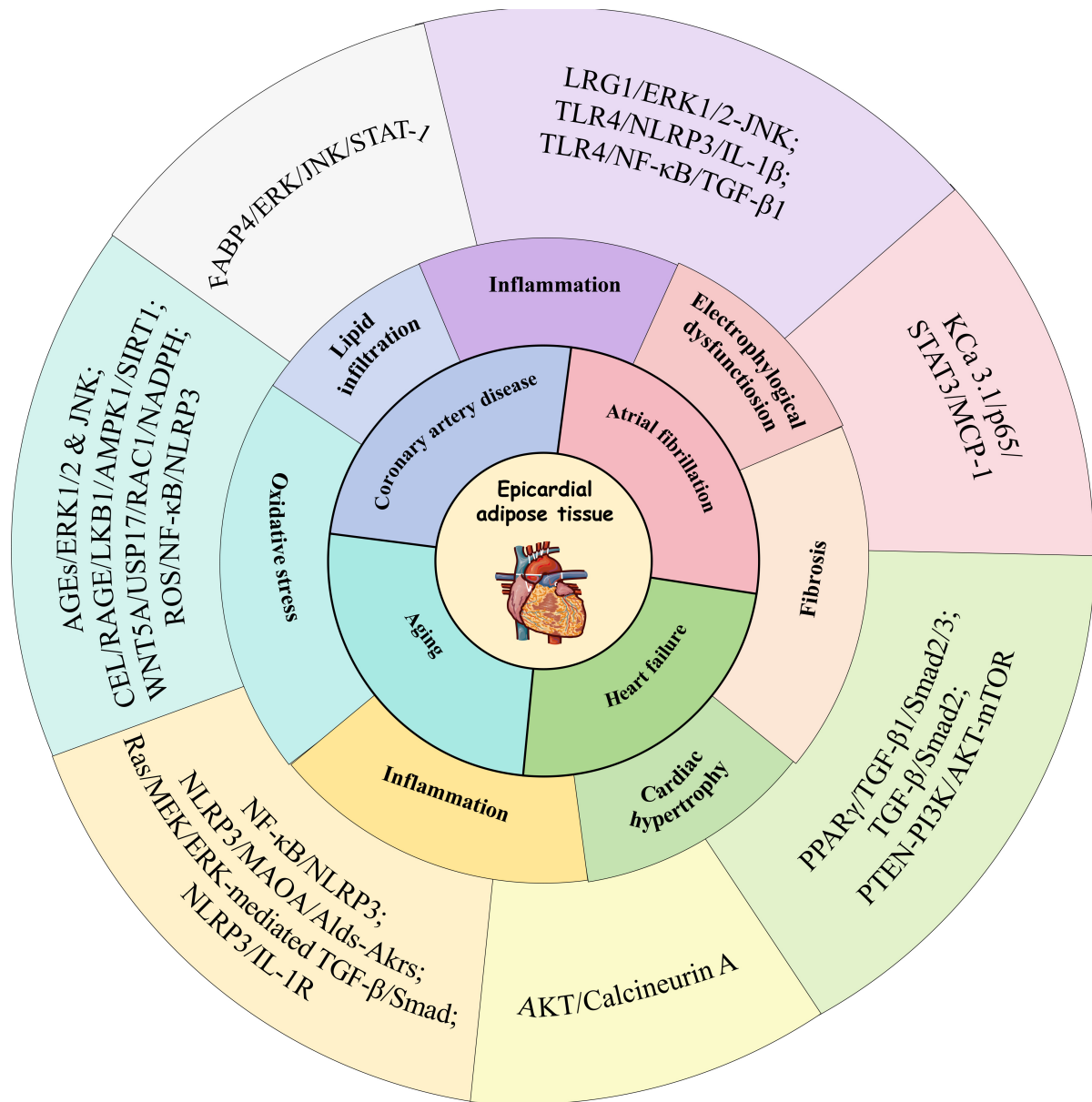


Figure 3. Mechanistic pathways linking EAT dysfunction to CVD and aging. The pathological expansion and dysfunction of EAT promote inflammatory responses, lipid infiltration, and fibrosis in the cardiac microenvironment through complex signaling cascade networks. These pathways contribute to the development of significant clinical outcomes, including CAD, AF, and HF. AF: Atrial fibrillation; CAD: coronary artery disease; CVD: cardiovascular disease; EAT: epicardial adipose tissue; HF: heart failure; FABP4: fatty acid-binding protein 4; NF- κ B: nuclear factor κ B; TGF- β : transforming growth factor- β ; AGEs: advanced glycation end products; JNK: Jun N-terminal kinase; ROS: reactive oxygen species; mTOR: mammalian target of rapamycin; RAGE: receptor for advanced glycation end products; LKB1: liver kinase B1; AMPK1: AMP-activated protein kinase 1; SIRT1: sirtuin 1; WNT5A: wingless-related integration site 5A; USP17: ubiquitin-specific protease 17; NADPH: nicotinamide adenine dinucleotide phosphate; NLRP3: NOD-like receptor family pyrin domain-containing 3; PPAR γ : peroxisome proliferator-activated receptor γ ; PTEN: phosphatase and tensin homolog; PI3K: phosphatidylinositol 3-kinase; ERK: extracellular signal-regulated kinase; CEL: N ϵ -carboxyethyl-lysine; STAT1: signal transducer and activator of transcription 1; LRG1: leucine-rich alpha-2 glycoprotein 1; TLR4: toll like receptor 4; IL: interleukin; MCP: monocyte chemoattractant protein; MAOA: monoamine oxidase A; Alds: aldehyde dehydrogenases; Akrs: aldo-keto reductases; Ras: rat sarcoma; MEK: mitogen-activated protein kinase kinase.

increase lipid infiltration into coronary arteries, thereby contributing to lipotoxicity^[36]. Fatty acid-binding proteins (FABPs), particularly adipocyte fatty acid-binding protein 4 (FABP4), play a crucial role in intracellular FA transport and metabolism, thereby mediating lipotoxic and pro-atherogenic effects that correlate with myocardial ischemia and atherogenic dyslipidemia. Oxidized low-density lipoprotein (LDL)

Table 2. Role of EAT in CVD

CVD	Subtype	Alteration of EAT	Mechanism of EAT	Reference
CAD	Vulnerable plaque/ACS	• ↑EAT thickness; • ↑EAT volume; • ↑FAI	• Inflammation: ↑M1 macrophage polarization; ↑Cytokines (IL-6, MCP-1); • Lipotoxicity: ↑FFAs; ↑FABP4; • Oxidative stress: ↑NADPH oxidase activity; ↑ROS	[36,60,72,73,96-103]
	AF/AF recurrence	• ↑Total EAT volume in AF recurrence; • ↓Total EAT attenuation/density in AF recurrence; • ↑LA EAT attenuation/density in AF	• Fibrosis; • Inflammation: ↑Pro-inflammatory cytokines and adipokines (leptin, MCP-1, IL-6); • ↑macrophage migration; • Electrophysiological dysfunction	[36,50,66,82-84,104-108]
Arrhythmias	Ventricular arrhythmias	• ↑EAT thickness; • ↑EAT volume	• Inflammation: inflammatory immune cell infiltration/activation; pro-inflammatory macrophage phenotype; • Lipid metabolic alteration; • Fibro-fatty remodeling	[109-111]
	HFpEF	• ↑EAT thickness; • ↑EAT volume; • ↓EAT entropy		[81,112-115]
HF	HFmrEF	Inconsistent findings in EAT thickness	• Fibrosis • Inflammation: ↑M1 macrophage polarization; ↑pro-inflammatory factors (TNF-α, IL-1β);	[114,115]
	HFrfEF	• Inconsistent findings in EAT thickness; • ↓EAT volume	• Cardiac hypertrophy	[112,114-116]
	HFimpEF	↓EAT volume		[117]

Arrow symbols: (↑ for increase, ↓ for decrease). AF: Atrial fibrillation; CAD: coronary artery disease; CVD: cardiovascular disease; EAT: epicardial adipose tissue; FABP4: fatty acid-binding protein 4; FAI: fat attenuation index; FFAs: free fatty acids; HF: heart failure; HFrfEF: heart failure with reduced ejection fraction; HFimpEF: heart failure with improved ejection fraction; HFmrEF: heart failure with mildly reduced ejection fraction; HFpEF: heart failure with preserved ejection fraction; IL-6: interleukin-6; MCP-1: monocyte chemoattractant protein-1; ROS: reactive oxygen species; TNF- α : tumor necrosis factor- α ; ACS: acute coronary syndrome; NADPH: nicotinamide adenine dinucleotide phosphate; IL-1 β : interleukin-1 beta.

induces FABP4 expression in mononuclear and endothelial cells (ECs). FABP4 upregulates the extracellular signal-regulated kinase (ERK)/c-Jun N-terminal kinase (JNK)/signal transducer and activator of transcription 1 (STAT-1) signaling pathways, while downregulating endothelial nitric oxide synthase (eNOS) and stromal cell-derived factor-1 (SDF-1) pathways, ultimately leading to endothelial dysfunction^[100]. Increased NAD(P)H oxidase activity and oxidative stress contribute to the inflammatory pathophysiology of diabetes-associated CAD. In diabetes complicated by atherosclerosis, advanced glycation end products (AGEs) induce phosphorylation of mitogen-activated protein kinases (MAPKs), such as ERK1/2 and JNK, leading to upregulation of redox-sensitive inflammatory gene expression, such as IL-6 and MCP-1^[101]. In obesity-associated atherosclerosis, AT-derived wingless-related integration site 5A (WNT5A) promotes vascular oxidative stress via the ubiquitin-specific protease (USP) 17/RAC1/NADPH oxidase signaling axis, thereby facilitating redox-sensitive vascular smooth muscle cell migration^[119]. Notably, inflammation is a prominent feature of EAT in patients with CAD^[19] and is particularly evident in acute coronary syndrome (ACS), which exhibits higher levels of vascular inflammation compared to stable angina pectoris (SAP)^[120].

To further examine the relationship between EAT inflammation and coronary atherogenesis, Hirata *et al.*^[97] analyzed the dynamics of macrophage polarization. Their findings demonstrated that the EAT inflammatory status is primarily determined by macrophage polarization rather than the absolute number of infiltrating macrophages. In patients with CAD, EAT shows significantly increased macrophage infiltration, with a predominance of pro-inflammatory M1 macrophages (CD11c⁺) over anti-inflammatory M2 subsets (CD206⁺

). This phenotypic shift toward inflammation was positively correlated with CAD severity ($r = 0.312$, $P < 0.05$). In addition, Wang *et al.*^[121] indicated that leucine-rich alpha-2 glycoprotein 1 (LRG1) accelerates atherosclerosis progression by inducing pro-inflammatory M1-like macrophage polarization through the activation of ERK1/2 and JNK signaling pathways. Furthermore, the analysis of differentially expressed genes (IL-1 β , IL-6, MCP-1, and TNF- α) revealed upregulation of inflammatory and immune response-related genes in EAT, whereas adipocyte-related genes were downregulated^[54]. These gene expression changes may be attributable to fibrosis and cell apoptosis in EAT during the advanced stages of organ disease^[36].

The pathogenesis of ACS is closely associated with inflammatory responses. Following MI, infiltrating neutrophils activate the toll like receptor 4 (TLR4)/NOD-like receptor family pyrin domain-containing 3 (NLRP3)/IL-1 β signaling pathway by releasing S100A8/A9, which stimulates granulopoiesis in a cell-autonomous manner^[122]. In atherosclerosis complicated by type 2 diabetes mellitus (T2DM), N ϵ -carboxyethyl-lysine (CEL), a major AGE, impairs macrophage autophagy via the receptor for AGE/Liver Kinase B1/AMP-activated protein kinase 1 (AMPK1)/Sirtuin 1 signaling pathway, thereby promoting plaque instability, characterized by necrotic core expansion and an increased risk of rupture^[123]. Furthermore, matrix metalloproteinases (MMPs) secreted by EAT can degrade the fibrous caps of coronary plaques, leading to plaque instability and the development of ACS^[60]. Collectively, EAT contributes to CAD through multiple mechanisms, including increased lipid infiltration, oxidative stress, and inflammation [Figure 3].

A retrospective cross-sectional study found that EAT thickness was significantly greater in patients with ACS compared to those without ACS ($P = 0.035$)^[99]. A recent multicenter serial CCTA study demonstrated that higher EATv was independently associated with both plaque progression and rapid plaque progression even after adjusting for conventional cardiovascular risk factors. Furthermore, patients with higher EATv exhibited greater progression of both calcified and non-calcified plaque components, underscoring the importance of CT-derived EAT quantification for identifying individuals at increased risk of adverse coronary plaque evolution^[124]. Gao *et al.*^[60] reported that, compared with EATv, EAT density (cut-off: -111.50 HU) exhibited stronger predictive value for early diagnosis and risk stratification of ACS.

FAI has been previously identified as a biomarker of coronary vascular inflammation. For example, coronary FAI identifies inflammatory risk in patients with non-obstructive CAD, even when visible plaques or coronary calcification are absent^[73]. Evidence indicates that plaque vulnerability is a more critical determinant of subsequent coronary occlusion than the degree of vascular stenosis^[103,125]. FAI may also assist in identifying inflamed, vulnerable plaques in ACS settings^[72]. In patients who developed ACS, culprit lesion precursors exhibited significantly higher PCAT attenuation than non-culprit lesions in the same patients and than lesions in patients with stable CAD^[96]. This finding suggests that vascular inflammation contributes to increased lesion instability and a higher risk of atherosclerotic plaque rupture^[96,126]. Furthermore, perivascular FAI values were significantly higher in culprit lesions than in control lesions, reinforcing its role as a surrogate marker for high-risk plaques, particularly when combined with other CCTA markers of plaque inflammation, such as plaque enhancement and the napkin-ring sign^[103]. Additionally, Overgaard *et al.*^[98] reported that among patients with T2DM without symptoms or a prior diagnosis of CAD, high PCAT attenuation (≥ -70.1 HU) uniquely predicts progression of non-calcified plaque burden, thereby supporting its role as a biomarker for the progression of subclinical atherosclerosis. Furthermore, high perivascular FAI values (cut-off ≥ -70.1) are independent predictors of all-cause and cardiac mortality^[74].

CAC serves as a marker of atherosclerotic burden by detecting calcified coronary plaques, thereby potentially guiding pharmacological and lifestyle interventions to prevent CAD^[127,128]. Numerous studies have examined the correlation between EAT and CAC; however, the findings remain inconsistent^[129-133]. Several studies have reported a positive association. For instance, de Vos *et al.*^[130] demonstrated that PCAT thickness was

positively correlated with coronary calcification in healthy postmenopausal women ($P = 0.026$). Similarly, in a retrospective cross-sectional study of individuals with diabetes, Cosson *et al.*^[129] reported a positive association between EATv and CAC, potentially reflecting the early pathophysiological impact of EAT on local atherosclerosis. Furthermore, Eisenberg *et al.*^[21] observed that asymptomatic patients with both an EATv $\geq 113 \text{ cm}^3$ and CAC $\geq 100 \text{ AU}$ exhibited the highest risk of MACE. However, other studies have reported that the correlation between EAT and CAC is either weak after adjustment for cardiovascular risk factors or not statistically significant in certain populations^[131-133]. Therefore, further investigation is warranted to clarify the association between EAT and CAC, given its potential clinical implications for understanding the progression of subclinical coronary atherosclerosis.

EAT in the development of arrhythmias

AF

Fibro-fatty infiltration of the atrial sub-epicardium represents a critical substrate for AF^[134]. Accumulation and fibro-fatty modifications in EAT surrounding the atria are associated with increased risk, persistence, and clinical severity of AF^[11]. Additionally, patients with permanent AF exhibit predominant fibro-fatty infiltration and extensive fibrotic remodeling^[135].

In patients with AF, hsa-miR-548ay-3p expression in EAT is significantly upregulated. Experimental evidence from both *in vitro* and *in vivo* studies confirms that hsa-miR-548ay-3p induces adipocytokine dysregulation by targeting PPAR γ . This dysregulation subsequently promotes myocardial fibrosis via the transforming growth factor- β 1 (TGF- β 1)/Smad2/3 signaling pathway^[105].

EAT functions as a mediator of cardiac and systemic inflammation^[36,46], contributing to the pathogenesis of AF through secretion of various pro-inflammatory and pro-fibrotic adipokines and cytokines, including leptin, visfatin, MCP-1, and IL-6^[35,101]. For example, leptin modulates calcium handling, regulates neuroendocrine function, promotes pro-fibrotic remodeling, and facilitates arrhythmic phenotypes^[36,107]. Sun *et al.*^[136] reported that C-reactive protein (CRP) inhibits proliferation and induces apoptosis in HL-1 cardiomyocytes by activating TLR4, increasing pro-inflammatory factor expression such as IL-6, and facilitating crosstalk between TLR4 and the NF- κ B/TGF- β 1/Smad2 signaling pathways, suggesting a potential role in inflammation-mediated AF. In the transition zone between atrial subepicardial adipocytes and fibrotic tissue, inflammatory cell infiltration occurs, mainly involving CD3⁺ T lymphocytes, primarily CD8⁺ cytotoxic T cells, with fewer CD20⁺ B lymphocytes, scattered CD14⁺ monocytes, and CD15⁺ neutrophils^[135]. Additionally, local EAT macrophages may further increase AF susceptibility by migrating to the adjacent atrium. Under rapid pacing conditions, macrophage infiltration in the atrium adjacent to EAT is increased and accompanied by electrical remodeling, potentially mediated by myocardial KCa3.1-dependent regulation of CCL2 secretion via the p65/STAT3 signaling pathway^[104]. Notably, EVs derived from EAT of patients with AF exhibit significantly reduced levels of IL-10 and vascular endothelial growth factor (VEGF). Specific pathways associated with atrial fibrosis and hypertrophy, such as TGF- β and 5-hydroxytryptamine (5-HT), are uniquely expressed in EVs from patients with AF^[106].

EAT may contribute to arrhythmogenesis by modulating ionic currents, altering gap junctional coupling, and promoting electrophysiological remodeling^[50]. In a clinical study examining the potential mechanisms by which EAT may modulate the atrial substrate for AF, Nalliah *et al.*^[108] reported that local accumulation of EAT and myocardial infiltration were clinically associated with atrial conduction abnormalities and structural remodeling. Additionally, *ex vivo* and *in vitro* studies further showed that EAT impairs atrial electrophysiology through mechanisms such as myocardial infiltration and paracrine signaling, as evidenced by slowed conduction and prolonged field potential duration. Collectively, these findings suggest that EAT contributes to the occurrence of AF through multiple interconnected mechanisms, including inflammation,

fibrosis, and electrophysiological remodeling [Table 2 and Figure 3].

In addition to elucidating the mechanistic role in AF pathogenesis, advanced imaging techniques have been employed to assess dynamic changes in the EAT before and after AF ablation and to evaluate its prognostic value for predicting AF recurrence [Figure 1]^[84,137,138]. Chamoun *et al.*^[138] conducted a longitudinal Magnetic resonance imaging (MRI) study demonstrating a 46% relative reduction ($P < 0.001$) in the volume of LA EAT post-ablation. This finding suggests that potential mechanisms underlying post-ablation EAT alterations include direct thermal effects, microvascular disruption, ablation-induced inflammatory responses, and reduced arrhythmias burden. A greater absolute median reduction in EAT was observed in patients with persistent AF than in those with paroxysmal AF. Furthermore, they proposed that alterations in LA EAT may influence the evolution of the AF substrate following catheter ablation, potentially affecting arrhythmias recurrence. Additionally, a retrospective study from two high-volume centers utilizing pre-ablation CT assessment demonstrated that EATv and EAT attenuation are associated with the risk of recurrence after ablation. Patients with AF recurrence exhibited significantly higher total EATv and lower EAT attenuation values^[84].

Ventricular arrhythmias

Arrhythmogenic cardiomyopathy (ACM) is a genetic disorder characterized by progressive fibro-adipose replacement of the ventricular myocardium, which clinically manifests as ventricular arrhythmias (VA) and sudden cardiac death^[110,139]. The mechanisms underlying changes in EAT deposition in ACM remain poorly understood. Studies have shown that patients with ACM exhibit increased EAT thickness around the ventricles and that EAT expansion is associated with disease progression^[110]. To investigate the potential alterations in lipid metabolism among ACM patients, Cui *et al.*^[109] examined the pathological features, fat lineage, and lipid profiles of fibro-fatty tissues in ACM. Their analysis of brown, beige, and white fat marker expression in RV fibro-fatty tissues revealed that fat predominantly accumulates in the sub-epicardium, followed by the mid-wall. This subepicardial distribution may result from the epicardium's heightened sensitivity to adipogenic stimuli and the ability of EAT to transition from providing metabolic support to promoting inflammation^[46]. Consistently, fibro-fatty tissues in ACM demonstrate elevated saturated TG levels and significant infiltration by inflammatory immune cells. Subsequent immune profiling further identified an accumulation of pro-inflammatory macrophages expressing elevated levels of cytokines and chemokines, including CCL3, suggesting that inflammatory remodeling within fibro-fatty tissues likely contributes to myocardial injury and disease progression in ACM^[109].

A study examining the relationship between EATv and the incidence of malignant ventricular arrhythmias (MVA), including sustained ventricular tachycardia (VT), ventricular fibrillation (VF), or appropriate implantable cardioverter-defibrillator (ICD) shock, by Mahmoud *et al.*^[111] found that patients with MVA exhibited a significantly higher BMI ($P = 0.006$), a lower left ventricular ejection fraction (LVEF, $P < 0.001$), and an increased ventricular EATv ($P < 0.001$) compared to those without MVA. Additionally, the study further demonstrated that each 10 mL/m² increment in EATv was associated with a 97% higher incidence of MVA ($P < 0.001$) and identified 55.6 mL/m² as the optimal ventricular EATv cut-off for predicting MVA incidence. Additionally, these findings also suggest that ventricular EAT accumulation may increase susceptibility to MVA in individuals with the phospholamban (PLN) p.(Arg14del) variant. In summary, alterations in EAT and the proposed mechanisms underlying VA are detailed in Table 2.

EAT in the development of HF

HF is classified into four subtypes based on LVEF: HF with preserved ejection fraction [HFpEF, LVEF $\geq 50\%$ with evidence of spontaneous or provokable increased left ventricular (LV) filling pressures]; HF with mildly reduced ejection fraction (HFmrEF, LVEF 41%-49% with evidence of spontaneous or provokable increased

LV filling pressures); HF with improved ejection fraction (HFimpEF, previous LVEF $\leq$ 40% and a follow-up measurement of LVEF $>$ 40%); and HF with reduced ejection fraction (HFrEF, LVEF $\leq$ 40%)^[140]. Notably, with an aging population and rising obesity prevalence, HFpEF is becoming more common worldwide^[113]. Obesity-related HFpEF represents a high-risk phenotype across the HFpEF spectrum^[141] and is characterized by greater concentric remodeling^[142]. Accumulating evidence suggests that EAT contributes to HFpEF via multiple mechanisms, including pro-inflammatory paracrine effects^[143], lipotoxicity due to toxic lipid intermediates such as DAGs and ceramides^[143,144], and adverse mechanical effects such as pericardial restraint^[143,145], which may promote myocardial fibrosis and diastolic dysfunction^[46,143]. However, whether EAT plays a causal role in the pathophysiology of HFpEF or acts as a passive bystander remains unclear^[29].

To explore the processes contributing to the transition from adaptive cardiac hypertrophy to HF under pressure overload, Yu *et al.*^[146] established a transverse aortic constriction (TAC)-induced model of cardiac hypertrophy and HF, demonstrating that early neutrophil infiltration upregulates S100A8/A9, activating the p38 MAPK/JNK/AP-1 signaling pathway and promoting the production of the inflammatory cytokine IL-1 β and the chemokines CCL2 and CCL6. These chemokines facilitate the recruitment of CCR2⁺ macrophages into the injured myocardium. Subsequently, infiltrating CCR2⁺ macrophages exhibit increased S100A8/A9 expression, further amplifying myocardial inflammation via activation of the NF- κ B/NLRP3 pathway. In parallel, S100A8/A9 promotes cardiac hypertrophy and fibrosis through AKT/calcineurin A and TGF- β /Smad2 signaling pathways. In addition, Yang *et al.*^[147] demonstrated that B lymphoma Mo-MLV insertion region 1 homolog, a transcriptional repressor, promotes cardiac fibroblast proliferation and migration through regulation of phosphatase and tensin homolog (PTEN)/phosphatidylinositol 3-kinase (PI3K)/AKT/mammalian target of rapamycin (mTOR) signaling pathways. Collectively, these pathways represent inflammatory and profibrotic mechanisms relevant to HF pathobiology and intersect with EAT-associated remodeling [Figure 3 and Table 2].

Numerous studies have reported inconsistent associations between EAT and cardiac function in patients with HF^[112,114,115,117,148]. Among the various HF phenotypes, patients with HFpEF generally exhibit the greatest EAT thickness^[112,114]. However, evidence regarding EAT thickness in HFmrEF remains inconclusive. Rossi *et al.*^[115] reported that EAT thickness in patients with HFmrEF was comparable to that in patients with HFpEF. In contrast, Jin *et al.*^[114] reported no significant difference in EAT thickness between patients with HFmrEF and those with HFrEF, with both groups exhibiting lower EAT thickness than patients with HFpEF. Therefore, it remains unclear whether EAT thickness is significantly lower in HFrEF than in HFmrEF^[114,115]. The clinical implications of EAT thickness may vary across HF phenotypes. In patients with HFpEF, increased EAT thickness is associated with adverse cardiovascular hemodynamics, an unfavorable metabolic profile, and worse prognosis^[112]. Conversely, in patients with HFmrEF/HFrEF, greater EAT thickness appears to be associated with better left cardiac function^[112,114].

In addition to assessing EAT thickness, research has focused on the relationship between EATv and HF. Menghoum *et al.*^[113] reported that patients with HFpEF had greater EATv compared to controls or patients with preclinical HF (American College of Cardiology/American Heart Association classification; ACC/AHA stage B). Conversely, Doesch *et al.*^[116] observed that patients with compensated symptomatic congestive HF and LV systolic dysfunction, defined as LVEF $\leq$ 35%, had lower EATv than healthy controls. According to Yang *et al.*^[117], during a median follow-up of 8.6 months, 51.2% of patients with HFrEF developed HFimpEF. Compared to patients with persistent HFrEF, those who developed HFimpEF demonstrated significantly lower EATv ($P < 0.001$) and higher EAT density ($P < 0.001$). Based on these findings, the authors proposed that moderate inflammation within EAT may promote myocardial repair and LV reverse remodeling; however, this hypothesis requires further validation.

In addition to volume, the density and entropy of EAT may have significant clinical implications. Liu *et al.*^[149] reported that, among patients with HFpEF, lower EAT density was associated with a higher cumulative incidence of HF readmission and composite clinical endpoints ($P < 0.05$). Similarly, a retrospective cohort study^[81] demonstrated that both LV EAT volume and entropy independently predicted incident HFpEF in patients with MI, preserved LVEF, and no prior percutaneous coronary intervention. Notably, EAT entropy may provide a complementary measure to volume-based assessments, as patients who developed HFpEF exhibited significantly lower EAT entropy. This finding indicates reduced heterogeneity of EAT tissue composition, which may reflect the predominance of WAT and the decreased metabolic activity of protective BAT. Collectively, these findings suggest that changes in EAT quantity and heterogeneity may be linked to inflammatory activation and diastolic dysfunction, potentially contributing to the development of HFpEF. At the molecular level, Frisk *et al.*^[150] identified 18 differentially expressed genes in the EAT between patients at risk for HF (ACC/AHA stage A) and those with pre-HF (ACC/AHA stage B), suggesting that distinct EAT molecular signatures may arise during the early transition toward HF.

EAT IN CARDIOVASCULAR AGING

The measurement of EAT may facilitate early detection of age-related physical decline^[151]. AT enlargement in obesity can result in hypoxia, a driver of aging-related processes. Mandl *et al.*^[17] showed that expression of acyl-CoA synthetase long-chain family 4 (ACSL4) is associated with brown-like adipogenesis, whereas hypoxia downregulated ACSL4 protein levels in Simpson-Golabi-Behmel Syndrome organoids and induced an inflammaging phenotype. In human EAT samples, ACSL4 mRNA expression was positively correlated with UCP1 and hypoxia-inducible pro-inflammatory markers, whereas ACSL4 protein expression exhibited an inverse trend. These findings indicate a relationship between brown-like adipogenesis, hypoxia-related inflammatory signaling, and ACSL4-mediated ferroptotic capacity in EAT.

At the level of immune regulation, recent studies have highlighted the essential role of immune cells within AT. Yu *et al.*^[152] demonstrated that aging is associated with persistent accumulation of immunoglobulin G (IgG) in AT, partially driven by adipose-infiltrating B cells. This IgG accumulation activates macrophages via the Rat sarcoma (Ras)/mitogen-activated protein kinase (MEK)/ERK signaling pathways and subsequently promotes WAT fibrosis through the TGF- β /Smad pathway. Furthermore, during aging, NLRP3 inflammasome-dependent inflammation contributes to the expansion of aged adipose B cells in VAT. These B cells express the IL-1 receptor, and inhibition of IL-1 signaling reduces their proliferation and enhances lipolysis, suggesting that IL-1 signaling drives the expansion of aged adipose B cells and contributes to AT metabolic dysfunction^[153]. Additionally, Camell *et al.*^[154] identified a neuro-immune mechanism linking age-related chronic inflammation to impaired AT lipolysis. Specifically, NLRP3 inflammasome activation in ATMs during aging upregulates growth differentiation factor 3 (GDF3) and genes involved in catecholamine-catabolism, including monoamine oxidase A (MAOA), catechol-O-methyl-transferase (COMT), and members of the aldehyde dehydrogenases (Alds) and aldo-keto reductases (Akr) families. This process promotes norepinephrine (NE) degradation, reduces NE availability in VAT, and ultimately attenuates catecholamine-induced lipolysis. Although this study primarily examined VAT, these findings offer mechanistic insights into the immune-metabolic remodeling of EAT during aging.

AT is particularly susceptible to aging and undergoes significant alterations in distribution, cellular composition, and endocrine-immune function. During aging, AT exhibits increased VAT deposition, reduced brown and beige fat activity, impaired function of adipose progenitor and stem cells, accumulation of senescent cells, and dysregulated immune-cell activity. Senescent cells secrete a senescence-associated secretory phenotype (SASP) that includes cytokines, chemokines, proteases, and growth factors, which act as aging-related signals. These changes contribute to impaired adipogenesis, inflammation, abnormal adipocytokine production, insulin resistance, and overall AT dysfunction^[18]. SASP factors act paracrinally on

adjacent cells and may also enter the systemic circulation, thereby promoting inflammaging^[1]. This systemic inflammatory environment can adversely affect cardiac function. For example, Liu *et al.*^[155] showed that increased cardiomyocyte NLRP3 inflammasome-mediated pyroptosis promotes D-galactose-induced cardiac aging. Their findings suggest that the ROS/NF- κ B/NLRP3 signaling loop facilitates cardiomyocyte senescence by promoting NLRP3 inflammasome activation, caspase-1-dependent pyroptosis, and IL-1 β release. This mechanism underscores the connection between oxidative stress, inflammatory cell death, and cardiac aging.

TARGETING EAT IN CVD

The specific mechanisms by which EAT contributes to the development and progression of CVD are complex. Debate persists on whether EAT functions as a direct “pathogenic mediator” driving disease via local paracrine effects or primarily serves as a “passive marker” of metabolic dysfunction. This topic has become a prominent focus in recent research. A prospective cohort study examined the association between epicardial and pericardial AT (EPAT) and the risk of developing T2DM, CAD, AF, and HF. Notably, the associations with T2DM, CAD, and HF were independent of BMI (though the AF association was not). Given the strong similarity between EPAT and abdominal VAT in clinical outcomes and genetic determinants, when both were included simultaneously in survival models, the association between EPAT and CVD outcomes was no longer significant, whereas VAT remained significantly associated with the development of T2DM, CAD, AF, and HF. These findings suggest that the observed associations between EPAT and incident CVD may reflect systemic effects of metabolically unhealthy visceral adiposity rather than local or paracrine effects^[156]. Nevertheless, while this result highlights the influence of systemic metabolic factors on EAT, emerging evidence indicates that EAT’s role extends beyond serving solely as a marker.

Increasingly, EAT has been identified as a local pathogenic mediator of CVD. As previously described, under metabolic dysregulation associated with obesity and aging, EAT undergoes functional and morphological changes, shifting from a protective role in physiological states to a pro-inflammatory, profibrotic, pro-atherogenic, and pro-arrhythmogenic phenotype in pathological conditions. In these pathological states, EAT functions as a local secretory adipose depot, releasing pro-inflammatory and profibrotic cytokines via paracrine or vasocrine mechanisms, thereby establishing a local inflammatory and fibrotic environment that influences adjacent cardiac structures, including the myocardium^[19]. Notably, EAT exhibits distinct phenotypic changes in HFpEF and HFrEF, each with potentially different pathophysiological and prognostic consequences. In HFpEF, EAT typically expands and becomes a significant source of pro-inflammatory adipokines, thereby promoting cardiac hypertrophy and fibrosis. For instance, increased leptin and decreased adiponectin concentrations are associated with prohypertrophic and profibrotic signaling and structural cardiac abnormalities. Conversely, in HFrEF, EAT mass is reduced, and this reduction is associated with adverse prognostic outcomes. This reduction may indicate decreased availability of EAT-derived cytoprotective adipokines, although adipokine regulation in HFrEF is likely to be more complex^[9].

Current evidence indicates that no therapies directly target EAT inflammation. Existing pharmacological interventions evaluated for EAT reduction primarily consist of glucose-lowering and lipid-lowering agents^[157], which may confer clinical benefits, in part, by inducing favorable changes in the EAT phenotype, secretome, and EAT-mediated inflammatory pathways^[29]. Foundational management strategies primarily include lifestyle interventions, such as exercise and dietary modification, pharmacological therapies with metabolic and anti-inflammatory effects, and bariatric surgery.

A single-center secondary analysis of a randomized clinical trial (RCT) involving 50 physically inactive individuals with abdominal obesity investigated changes in EAT and PAT mass following 12 weeks of endurance or resistance training. EAT mass decreased by 32% and 24% following endurance and resistance

training, respectively, with reductions significantly greater than in the non-exercise control group. In contrast, PAT mass reduction after endurance training was not significantly different from the non-exercise control group, whereas resistance training resulted in a 31% reduction in PAT mass compared to the non-exercise control group^[158]. These findings suggest that EAT is more responsive to exercise than PAT, potentially due to higher IL-6 receptor expression in EAT, although the small sample size should be considered^[159]. Furthermore, a systematic review and meta-analysis including 34 studies (10 suitable for meta-analysis) demonstrated that exercise interventions effectively reduced EATv, with a significant pooled effect size favoring exercise over control. The pooled analysis also favored pharmaceutical interventions to reduce EATv, although heterogeneity was substantial and not all individual pharmaceutical studies showed significant reductions^[160].

Pharmacological agents targeting EAT and PCAT include statins, glucagon-like peptide-1 (GLP-1) receptor agonists, and sodium-glucose cotransporter 2 (SGLT2) inhibitors^[25]. A subanalysis of an RCT involving 420 hyperlipidemic postmenopausal women with available CT scans demonstrated significant regression of EATv following one year of intensive atorvastatin therapy (80 mg/day), whereas moderate-intensity pravastatin therapy (40 mg/day) did not produce comparable results. This regression was not associated with reductions in LDL cholesterol and may be attributable to other statin effects, such as anti-inflammatory properties, although this remains speculative^[161]. Consistently, Raggi *et al.*^[162] reported that statins decreased EAT attenuation values by approximately 6% ($P < 0.001$), independent of LDL cholesterol lowering intensity, while SAT was unaffected. These findings suggest that decreased EAT attenuation values may reflect reduced metabolic activity due to lower cellularity, vascularity, or inflammation; however, their clinical significance and underlying mechanisms require further investigation.

GLP-1 receptor agonists and glucose-dependent insulintropic polypeptide (GIP) analogs may influence EAT by activating GLP-1 and GIP receptors, potentially promoting a favorable balance between increased adipogenesis and reduced ectopic fat accumulation^[163]. Supporting this, an open-label randomized controlled study suggested that liraglutide may have a direct and independent effect on EAT, although the influence of weight loss could not be excluded. In this study of 95 patients with T2DM and overweight or obesity {BMI ≥ 27 kg/m², hemoglobin A1c [HbA1c] $\leq 8\%$ } receiving metformin monotherapy, participants were randomized to receive liraglutide in addition to metformin or to continue metformin alone. Only the liraglutide group showed improvements in BMI and HbA1c during the 6-month follow-up. EAT thickness decreased by 29% and 36% at 3 and 6 months, respectively ($P < 0.001$), whereas no significant reduction was observed in the metformin monotherapy group^[164]. Additionally, the GLP-1 receptor agonist semaglutide (2.4 mg weekly) appears to improve several aspects of adverse cardiac remodeling compared with placebo over 52 weeks in patients with obesity-related HFpEF, including attenuation of LA volume progression, improvement in LV diastolic function, and reduction in RV size^[141]. Research indicates that the benefits of semaglutide in patients with obesity-related HFpEF and T2DM may extend beyond weight loss, potentially including direct effects on decongestion, vascular function, skeletal muscle, mitochondrial capacity, EAT, inflammation, and insulin resistance^[165]. Furthermore, in a prespecified secondary analysis of the study of therapeutic outcomes in patients randomized trial, Manubolu *et al.*^[166] found that, among participants with T2DM and known CAD, semaglutide treatment was associated with a 9% reduction in EATv ($P \leq 0.001$) and a 5% increase in mean EAT density compared with placebo in multivariate models. Tirzepatide, a long-acting dual GIP and GLP-1 receptor agonist, has limited data regarding its effects on EAT. Packer *et al.*^[167] found that, in patients with HFpEF and obesity, tirzepatide reduced the risk of the composite endpoint of adjudicated death from cardiovascular causes or worsening HF compared with placebo. In patients with obesity-related HFpEF, tirzepatide therapy reduced LV mass and paracardiac AT (epicardial and pericardial adipose tissue) volume, primarily by reducing PAT rather than EAT. Although tirzepatide did not produce a significant effect on EATv compared with placebo, it may modulate EAT biology in ways that are not detectable by CMR^[142].

It has been demonstrated that SGLT2 is expressed in EAT^[168], predominantly in epicardial preadipocytes, and that its expression decreases significantly as preadipocytes mature into adipocytes^[169]. SGLT2 inhibitors, such as empagliflozin, suppress differentiation and maturation of human epicardial preadipocytes and downregulate pro-inflammatory adipokines, including IL-6 and MCP-1, at both the messenger RNA and secreted protein levels. Collectively, these mechanisms may underlie the observed SGLT2 inhibitor-mediated reduction in EATv and the associated cardioprotective effects^[169]. Bao *et al.*^[170] demonstrated that SGLT2 inhibitors were more effective than GLP-1 receptor agonists in reducing EAT thickness in individuals with T2DM and/or obesity. Therefore, they recommended prioritizing SGLT2 inhibitors to reduce EAT thickness in individuals with impaired glucolipid metabolism, such as those with T2DM and/or obesity. In a prospective randomized controlled clinical trial, the effects of the SGLT2 inhibitor dapagliflozin on AT depots were evaluated by assessing AT thickness and 2-deoxy-2-^[18F]FDG uptake (including EAT, mediastinal fat, perirenal fat, and SAT) in patients with T2DM and stable CAD. After four weeks of dapagliflozin treatment, EAT thickness decreased significantly by 19%, and glucose uptake in the EAT during a hyperinsulinemic euglycemic clamp decreased by 21.6% ($P = 0.014$). No significant changes were observed in other fat depots, suggesting a selective effect of dapagliflozin on EAT in this cohort^[171]. Bouchi *et al.*^[172] reported that after 12 weeks of luseogliflozin treatment, EATv decreased from 117 (96-136) cm³ to 111 (88-134) cm³ ($P = 0.048$), may reduce cardiovascular events, particularly coronary artery events, partly through a reduction in EATv. The reduction in EATv was correlated with a decrease in CRP ($r = 0.493$, $P = 0.019$).

Jamaly *et al.*^[173] reported a 35% reduction in the risk of HF diagnosis among patients who underwent bariatric surgery during long-term follow-up compared with those receiving standard care. The cardiovascular benefit following bariatric surgery may be partially, and speculatively, attributed to a local decrease in EATv^[174,175]. Sorimachi *et al.*^[176] found that after a median follow-up of 5.3 years post-bariatric surgery, the abdominal VAT area decreased by 30% in the subgroup assessed with abdominal CT, and EAT thickness decreased by 14% in the overall population (both $P < 0.0001$). Although improvements were observed in ventricular remodeling, longitudinal biventricular mechanics, and reduced pericardial restraint, the LA structure and function deteriorated, as indicated by increased LA volume, reduced LA reservoir strain, and an elevated E/e' ratio, which estimates LV filling pressure. These findings should be interpreted with caution, as noted by the authors, because some increases in LA volume and the E/e' ratio may be attributable to normal aging and the absence of a control group. Overall, bariatric surgery appears to reduce EAT thickness, although the effects on cardiac structure and function differ by chamber and warrant further investigation.

CONCLUSION AND OUTLOOK

Recent advances in the biology and function of EAT have significantly enhanced our understanding of its influence on health and disease. Under physiological conditions, EAT maintains a beneficial relationship with the heart and supports myocardial function. In contrast, pathological states enable EAT to contribute to the development of CAD, arrhythmias, and HF, primarily through paracrine signaling and cardio-mechanical interactions involving the coronary arteries and myocardium. This review examines the bidirectional crosstalk between EAT and the cardiovascular system, elucidates the specific mechanisms by which EAT promotes CVD, and demonstrates that CVD progression exacerbates EAT pathology, potentially establishing a vicious cycle. Given EAT's central role, precise quantification and cardiovascular risk stratification are essential. Therefore, this review evaluates both conventional and novel imaging techniques, compares their respective advantages and limitations, and recommends selecting appropriate technologies based on specific clinical requirements.

Despite significant advancements in EAT research, several critical knowledge gaps remain. EAT undergoes a phenotypic switch in conditions such as obesity, aging, and CVD, transitioning from a protective to a pathogenic phenotype. This transition is primarily characterized by the loss of BAT-like activity and the emergence of pro-inflammatory WAT-like features. However, the specific mechanisms initiating this transformation remain incompletely understood.

EAT exhibits a unique mixed phenotype, incorporating features of WAT, BAT, and beige AT, suggesting substantial cellular and functional heterogeneity. Studies on WAT have shown that APC functional heterogeneity and intrinsic diversity are important determinants of AT remodeling. In obesity, specific fibro-inflammatory or anti-adipogenic APC subsets contribute to pathological remodeling, including fibrosis, inflammation, and reduced adipogenic capacity^[177]. These observations suggest that phenotypic transition in EAT may involve similar APC-mediated mechanisms, although direct evidence remains limited. Moreover, spatially specific regulators controlling the functions of different EAT regions, such as PCAT and myocardial EAT, have yet to be identified. Addressing these challenges requires integrating advanced methodologies, including spatial omics technologies and AI-based imaging and molecular analyses.

Emerging spatial omics approaches, such as spatial transcriptomics, proteomics, and metabolomics, provide advanced methodologies for investigating the molecular and cellular mechanisms underlying CVD. Spatial transcriptomics, when integrated with single-cell or single-nucleus RNA sequencing, enables the identification of adipocyte subpopulations. Spatial proteomics examines the distribution of proteins within cells and tissues, providing critical information about protein localization and functions. Spatial metabolomics maps the spatial distribution of metabolites, elucidates metabolic pathways and their spatial organization, and facilitates the identification of potential therapeutic targets^[178]. These technologies have recently been applied to EAT research. For instance, spatial transcriptomic analysis has demonstrated increased inflammatory and pro-fibrotic remodeling at the border zone between EAT and atrial tissue. The EAT border zone is characterized by fibroblast enrichment, reduced adipocyte abundance, and upregulation of inflammatory gene expression compared to deep EAT. These inflammatory and pro-fibrotic remodeling features are more pronounced in patients with AF^[179], highlighting regional heterogeneity within EAT and suggesting that EAT adjacent to the myocardium exhibits a more pro-inflammatory and pro-fibrotic phenotype.

Future research priorities include: (1) improving the precise quantification of EAT using novel technologies such as AI; (2) investigating regional heterogeneity to elucidate pathogenic mechanisms underlying EAT; (3) developing innovative therapies specifically targeting EAT; and (4) promoting early detection and intervention in high-risk asymptomatic individuals. Collectively, these initiatives may enhance the clinical utility of EAT in CVD risk stratification, prognosis, and management, ultimately supporting its integration into clinical practice.

DECLARATIONS

Authors' contributions

Contributed equally to this work and share the first authorship: Zhang J, An Z, Luo H

Conceptualized and structured the manuscript: Song X, Tian J, Zhang L

Wrote the initial draft: Zhang J

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Revised and edited the manuscript: Tian J

Availability of data and materials

Not applicable.

AI and AI-assisted tools statement

Not applicable.

Financial support and sponsorship

This work was supported by Beijing Anzhen Hospital High-Level Research Funding (2024AZB3003, 2025AZC2019, and 2025AZC2018), the Beijing Hospitals Authority's Ascent Plan (No. DFL20220603), the High-level Public Health Technical Talent Construction Project of Beijing Municipal Health Commission (Leading Talent-02-01), the Beijing Municipal Association for Science, and the Scientific and Technological Development Fund of Beijing Anzhen Hospital (AZYZR202305).

Conflicts of interest

Song X is the Guest Editor of the special issue entitled "Artificial Intelligence in Cardiovascular Aging and Disease" in *The Journal of Cardiovascular Aging*. Song X was not involved in any steps of editorial processing, notably including reviewer selection, manuscript handling, and decision-making. The other authors declare no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Written informed consent for publication was obtained from the patients for the use of their medical images presented in this manuscript. All identifying information has been removed to ensure patient anonymity.

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