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STATE-OF-THE-ART REVIEW

Uncovering the Role of Epicardial Adipose Tissue in Heart Failure With Preserved Ejection Fraction

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ABSTRACT

Heart failure with preserved ejection fraction (HFpEF) is the most common form of heart failure. Obesity is a modifiable risk factor of HFpEF; however, body mass index provides limited information on visceral adiposity and patients with similar anthropometrics can present variable cardiovascular risk. Epicardial adipose tissue (EAT) is the closest fat deposit to the heart and has been proposed as a biomarker of visceral adiposity. EAT may be particularly important for cardiac function, because of its location (under the pericardium) and because it acts as a metabolically active endocrine organ (which can produce both beneficial and detrimental cytokines). In this paper, the authors review the role of EAT in normal and pathologic conditions and discuss the noninvasive imaging modalities that allow its identification. This review highlights EAT implications in HFpEF and discuss new therapies that act on EAT and might also exert beneficial effects on the cardiovascular system. (JACC Adv 2023;2:100657) © 2023 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Heart failure (HF) is a multifaceted syndrome with the fastest growing incidence of cardiovascular diseases.[1] Most scientific societies have agreed on the universal classification of HF into: heart failure with reduced ejection fraction (HFrEF) (ejection fraction [EF] <40%), HF with mildly reduced EF (EF: 41%-49%), and heart failure with preserved ejection fraction (HFpEF) (EF: >50%).[2,3] Robust epidemiological evidence[4-8] reveals that more than half of patients with HF falls into the latter category and that these patients had a significantly increased risk of death and hospitalization. Most importantly, effective evidence-based therapies to prevent adverse events in HFpEF still remain elusive.

Obesity represents excess total body adipose tissue[9] and is one of the strongest predictors for HFpEF.[10] Although obesity increases the risk of cardiac ischemic injury, which may induce myocardial loss and depressed ventricular function, the most common disorder in the myocardium of obese people is HFpEF. Potential mechanisms are rather focused on systemic and local inflammation, interstitial fibrosis, and energy substrate utilization.[11]

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ABBREVIATIONS AND ACRONYMS

^{18}F-FDG = ^{18}F-fluorodeoxiglucose

AF = atrial fibrillation

CCT = cardiac computed tomography

CMR = cardiac magnetic resonance

EAT = epicardial adipose tissue

EVs = extracellular vesicles

FABP4 = fatty acid-binding protein 4

FFA = free fatty acid

GLP = glucagon-like peptide

HF = heart failure

HFpEF = heart failure with preserved ejection fraction

IL = interleukin

LV = left ventricle

SGLT2i = sodium-glucose co-transporter 2 inhibitors

Visceral obesity and higher epicardial adipose tissue (EAT) could be particularly prejudicial, since they act as metabolically active endocrine organs, increase inflammation and may be associated with endothelial dysfunction, myocardial fibrosis, and ventricular remodeling.[10] EAT has the strongest association with HFpEF,[12,13] compared with HFrEF. Patients with HFpEF have an increased EAT burden[14,15] and exhibit a biological shift toward the synthesis of pro-inflammatory cytokines. Higher EAT is associated with significantly greater impairments in hemodynamics, enhanced ventricular interdependence, reduced exercise capacity,[16] and most importantly, with poor prognosis.[17-19] Newer therapies that reduce the risk of several cardiovascular disorders, including HFpEF, have also demonstrated to exert parallel effects modifying the volume and biology of EAT.[20,21] In contrast, a divergent role of EAT has been described for HFrEF with most studies showing smaller quantities of EAT in those patients.[13,22] Furthermore, in HFrEF, worse prognosis is associated with lower amounts of adipose tissue.[14,23]

This review covers the role of the closest adipose tissue to the heart in HFpEF, its clinical implications and its (patho)physiological mechanisms. Special attention is made on noninvasive imaging techniques and different methods for EAT assessment. Ultimately, we present how newer HF therapies might act on EAT and its potential role as a new target in cardiovascular disease.

HIGHLIGHTS

- HFpEF is associated with a broad range of metabolic comorbidities, epicardial and intramyocardial fat expansion, and imbalances in adipocyte-associated pro-inflammatory cytokines.
- EAT can produce both beneficial and detrimental cytokines, which are easily transmitted to the myocardium via the vasa vasorum, paracrine function, and extracellular vesicles. Under certain stimuli, expanded and dysfunctional EAT shifts its biology and releases pro-inflammatory and fibrotic cytokines, thus fostering (and precipitating) HFpEF.
- SGLT2i reduce EAT volume, mute its pro-inflammatory characteristics, and reduce outcomes in large-scale definitively powered trials in HFpEF.

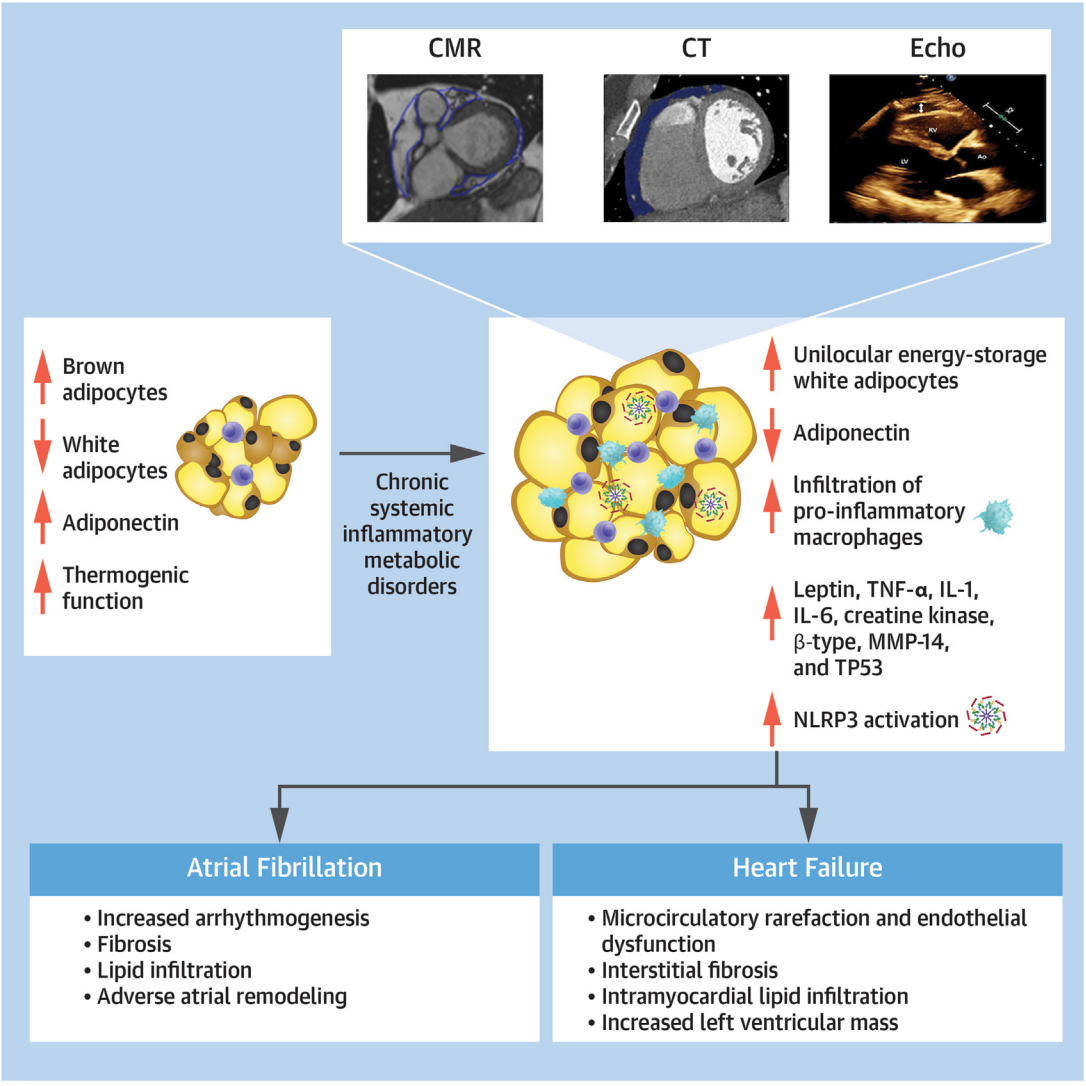
DEFINITION AND ANATOMY

EAT has a unique anatomic location between the myocardium and the visceral pericardium, immediately surrounding the heart and coronary arteries. It is mostly located in the atrioventricular and interventricular grooves but it also accumulates over the free wall of the right ventricle, left ventricular apex, and even almost the entire surface of the heart in some cases.[22] Without any barrier or muscle fascia in between, EAT shares a common microcirculation[24] with the underlying cardiac muscle and coronary arteries, thus facilitating a direct crosstalk between these structures. This is unique to EAT; no other visceral fat depot presents this contiguity with a target organ.[22] In contrast, paracardial adipose tissue is the visceral deposit located outside of the parietal pericardium. The composite of epicardial and paracardial fat is term pericardial fat.[25,26] Multiple terms have been used indistinctly in literature (intrathoracic, mediastinal, pericardial, or paracardial), thus leading to misconceptions. Distinction between epicardial and paracardial fat is important: paracardial adipose tissue has a different embryological origin, is not in direct contact with the heart, and is not vascularized by coronary arteries. Therefore, its effects on the myocardium are most likely different from those of EAT.[14]

HEALTHY AND PATHOLOGICAL EAT. In normal conditions, EAT participates in the homeostasis of the cardiovascular system as a metabolically active tissue with paracrine and exocrine functions, stores triglycerides that produce energy in the myocardium, and provides structural support preventing coronary arteries from twisting. Embryonically, it is also a major source of mesenchymal stem cells for cardiac regeneration.[27] However, in the presence of some inflammatory and metabolic disorders, such as obesity or diabetes, the epicardium becomes a site of pathological adipogenesis. EAT's biology can shift to a pro-inflammatory state: it creates more reactive oxygen species, less catalase, and different post-translational modifications of oxidative stress-related proteins compared with other adipose tissues.[28]

Adult EAT maintains brown fat-like and beige fat-like features, which are associated with improved cardiometabolic health.[29] Decline in brown fat-like features (in favor of more unilocular energy-storage white adipocytes) is associated with aging

CENTRAL ILLUSTRATION **Epicardial Adipose Tissue Inflammation is Associated With Atrial and Ventricular Dysfunction**



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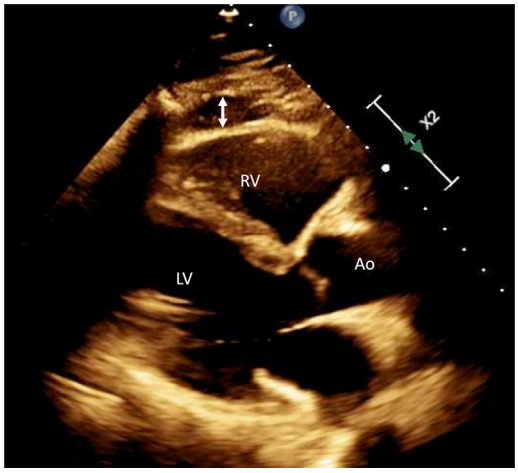
Epicardial adipose tissue expansion and inflammation has been suggested as a transducer between the derangements of systemic inflammation and atrial and ventricular dysfunction. CMR = cardiac magnetic resonance; CT = computed tomography; Echo = echocardiography; IL = interleukin; MMP = matrix metalloproteinase; TNF = tumor necrosis factor.

and accelerated in chronic diseases[29,30] (Central Illustration). Brown and beige adipose tissues utilize glucose and lipids to generate heat and EAT is thought to provide nonshivering thermogenesis and protection against hypothermia in the earliest stages of life. This function is mediated by uncoupling protein-1, a mitochondrial inner membrane protein which has been found to be considerably higher in EAT and essentially undetectable in other loci such as the subcutaneous adipose tissue.[22,31,32]

Another distinctive feature of EAT compared with other adipose tissues is its greater capacity for release and uptake of free fatty acids (FFAs), which are one of the main metabolic substrate of cardiomyocytes.[24] Fatty acid-binding protein 4 (FABP4), also known as

FIGURE 1 Transthoracic Echocardiography Allows to Measure the Thickness of the Epicardial Adipose Tissue But Not the Volume



Epicardial adipose tissue is marked by a white double-headed arrow. Ao = aorta; LV = left ventricle; RV = right ventricle.

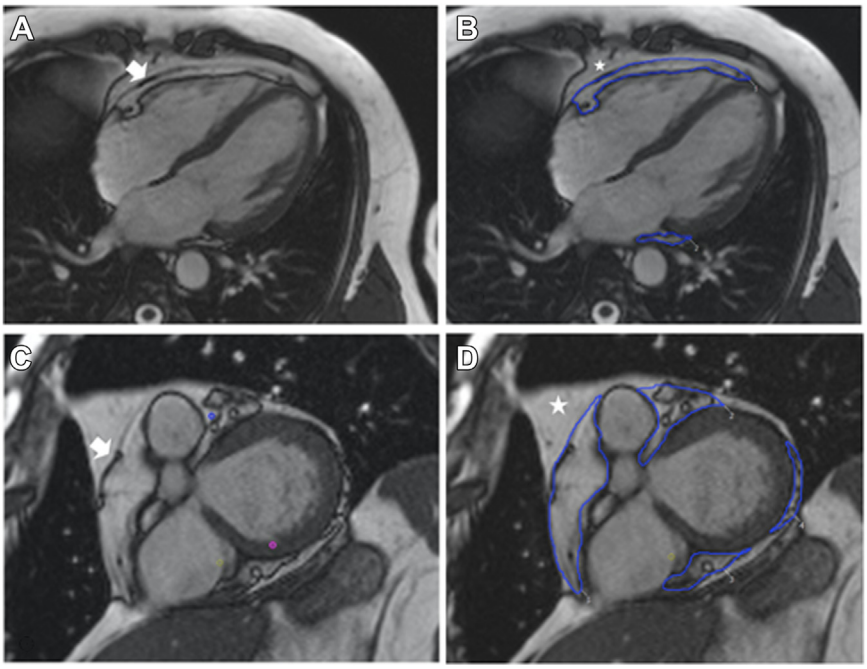
adipocyte protein-2, is highly expressed in EAT.[33] At the same time, FFAs seem to diffuse bidirectionally and can be recruited by EAT as a protective mechanism against lipotoxicity, similar to visceral adipocytes.[34]

ASSESSMENT BY NONINVASIVE IMAGING TECHNIQUES

Echocardiography has been the most widely used imaging technique given its widespread use in clinical practice[35] (Figure 1). However, it is hampered by the lack of volumetric data and the low sensitivity to differentiate between pericardial and epicardial compartments. Thickness and area (1- and 2-dimensional assessments of the epicardial space, respectively) might not be sensitive enough to capture temporal variations in EAT, especially in some clinical settings such as patient follow-up or treatment-induced changes. These measurements ignore the uneven geographical distribution of EAT along the heart and are more susceptible to greater interobserver and intraobserver variability.[36-38]

Volume quantification (3-dimensional assessment) is considered the most accurate estimation of EAT changes and burden,[38] and it can be estimated by both cardiac magnetic resonance (CMR) and cardiac computed tomography (CCT). On the one hand, CMR is radiation-free and allows the differentiation between epicardium and pericardium. The ability to visualize the motion of EAT throughout the cardiac cycle with conventional cine sequences (steady-state free precession) helps to discriminate between both tissues, even if the border is inconspicuous. CMR volumetric measurement of EAT using a "Simpson-like method" allows for a better quantification of EAT compared with the mere linear parameters more conventionally used (Figure 2). New MR techniques are in development, and currently, proton magnetic resonance spectroscopy allows the discrimination between FFA and unsaturated fatty acid deposition in the myocardium.[39] A promising area is the development of MR-based methods for identifying and distinguishing brown from white adipose tissue.[31] On the other hand, CCT allows a shorter imaging time and an accurate identification of adipose tissue using HU-based measurement, allowing for an objective quantification of EAT (Figure 3). Pixels accounted as fat based on a predefined HU window allow recognition of EAT (typically −195 to −45 HU),[40] even when filling in different and deeper heart areas. Moreover, inflammation can be detected as an increased EAT attenuation on CCT and it has been associated with cardiovascular disease[40] and has a high predictive value for cardiac mortality.[40-43] An imaging tool based on radiomics, termed perivascular fat attenuation index, has been designed to measure weighted gradients in the CCT attenuation of coronary perivascular fat. High perivascular fat attenuation index values (cutoff ≥−70.1 HU)[41-43] have prognostic value of increased cardiac mortality and, therefore, could help to implement early therapeutic approaches both in primary and secondary prevention. Although EAT and paracardial adipose tissue have different functional implications and thus an anatomical distinction is important, the combination of both (the so called pericardial fat tissue) has also been associated with an increased risk of HF, particularly HFpEF.[12] Although the role of the paracardial fat component in HF is not well-understood, pericardial fat (comprising both epicardial an paracardial) has been associated with coronary atherosclerotic plaques, which might explain its implications in the development of HF.[26] Novel imaging techniques are arising, and the use of ^{18}F-fluorodeoxiglucose (^{18}F-FDG) positron emission tomography (PET) is becoming more widespread, not only in the research setting but also for diagnosis of inflammation and infectious diseases.[44] ^{18}F -FDG is a glucose analogue and allows the identification of metabolic activity, which is considered an analogue for inflammation.[45] ^{18}F-FDG PET may be useful in the identification of EAT's inflammatory activity, which may have implications in different cardiovascular processes. In pericoronary fat, ^{18}F-FDG uptake is higher in patients with

FIGURE 2 Cardiac Magnetic Resonance Assessment of Epicardial Adipose Tissue



Imaging slices at the 4 chambers view (A and B) and the atrioventricular groove (C and D). Epicardial adipose tissue depots are outlined in blue. White arrow = pericardium; white stars = pericardial adipose tissue. Adapted with permission from Tromp et al.[13]

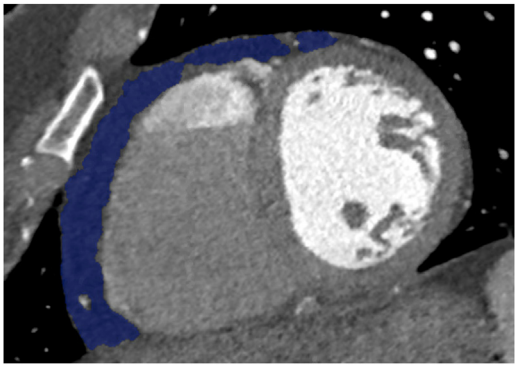
coronary artery disease.[46] Furthermore, the inflammatory activity of EAT located near the left atrium assessed by ^{18}F-FDG PET has been shown to be higher in patients with atrial fibrillation (AF) compared with controls.[47]

CLINICAL IMPLICATIONS OF EAT

Accumulation of EAT over the ventricles is associated with myocardial fibrosis, ventricular hypertrophy, and increased cardiac filling pressures, which are hallmark features of HFpEF.[16-19,48] Furthermore, the effects of EAT may be highly location-modulated,[49] with myocardial derangements residing in those segments that are immediately adjacent to areas of EAT with the greatest thickness. EAT over the right ventricle is associated with increased mass in the right ventricle, while EAT located over the left ventricle (LV) shows a similar association with left ventricular mass.[18] The pericoronary EAT seems to be more implicated in atherogenesis,[49] while the amount of adipose tissue accumulated around the atria is associated with the risk, persistence, and severity of AF.[50,51] Furthermore, it has even been observed a specific transcriptomic signature depending on its anatomical location (periatrial, periventricular, or pericoronary).[52] The location-modulated effects of EAT may have implications in cardiovascular outcomes; however, data in this area are still scarce.

Obese patients with HFpEF have some characteristics that differ from nonobese patients with HFpEF, including increased volume overload and biventricular remodeling.[11,17-19,48] These patients have greater pericardial restraint and increased ventricular interaction, contributing to higher left filling pressures. They may also have associated impaired pulmonary artery vasodilation, and higher pulmonary pressures would further exaggerate interventricular dependence.[11] Disproportionately low levels of natriuretic peptides characterize the phenotype of obesity-related HFpEF.[11] Cardiac or pericardial fibrosis and microcirculatory rarefaction may minimize wall stress and limit the capacity of the LV to enlarge in response to plasma volume expansion. Moreover, a decreased production (potentially linked to insulin resistance) and an augmented clearance (due to a higher expression of the clearance

FIGURE 3 Representative Example of Cardiac Computed Tomography Imaging



Epicardial adipose tissue is observed around right and left ventricles. Areas of epicardial adipose tissue are highlighted in blue.

receptors) have been suggested as additional mechanisms for the low levels of natriuretic peptides in these patients.[53]

Obesity and visceral adiposity have been linked to incident HFpEF,[54] but also to AF severity and recurrence.[55,56] AF is the most common arrhythmia in HFpEF patients occurring in one-third to one-half of all patients.[57] The pathogenesis of AF in HFpEF is believed to be partially driven by systemic inflammation,[58] but the mechanisms that link both entities are not yet completely understood. Volume of total pericardial adipose tissue quantified by CCT has been shown an independent predictor of AF even after adjusting for other risk factors,[59] and greater EAT volumes have been associated with a higher prevalence of AF and with higher recurrence rates after catheter ablation.[51,60] Furthermore, EAT can directly modulate the electrophysiology of atrial cardiomyocytes increasing arrhythmogenesis.[34,51,61] This association has generated the hypothesis that EAT may have a role in lipotoxicity-related ventricular arrhythmogenesis, but further investigation is warranted.

PATHOPHYSIOLOGICAL MECHANISMS

Augmented and dysfunctional EAT may exert 2 key detrimental effects on the heart: 1) cardiomechanical interaction; and 2) source of pro-inflammatory mediators.

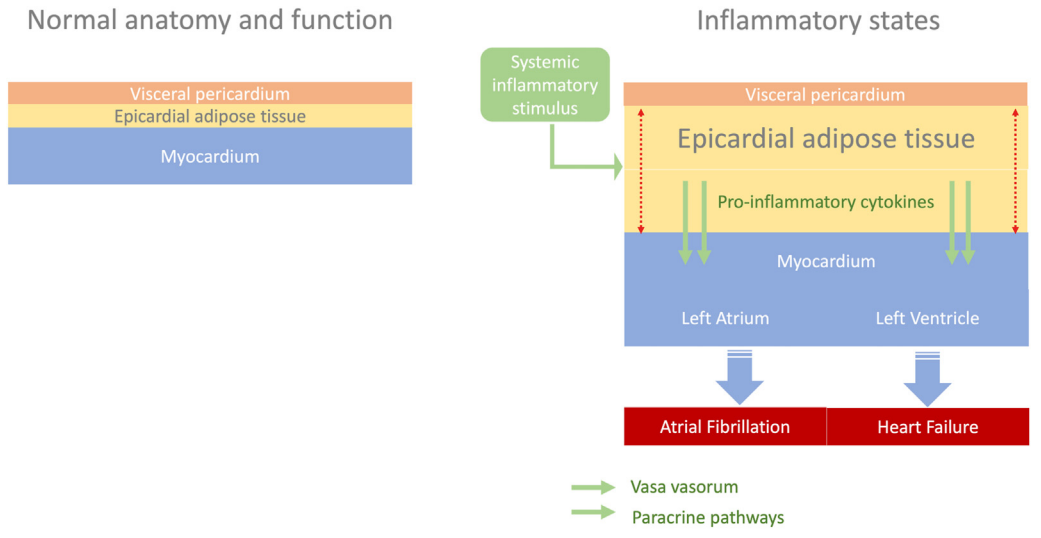
CARDIOMECHANICAL INTERACTION IMPAIRING VENTRICULAR COMPLIANCE. Expanded EAT in a limited space contributes to increased pericardial restraint and enhanced ventricular interdependence that have been described in the distinct obese phenotype of HFpEF.[11,16] Compared to nonobese patients and control subjects, obese patients with HFpEF present a greater increase in pericardial pressures both at rest and during exercise, which suggests increased pericardial restraint.[11] As EAT increases and ventricular interaction augments, the right and left ventricles compete for limited space in the pericardium, pressures equilibrate in both sides of the ventricle, and the septum becomes flattened and less convex to the right ventricle.[11,62] This causes ventricular interdependence and uncoupling between the LV filling pressure and LV preload. Greater LV filling pressures lead to higher pressure in the pulmonary capillaries, which contributes to dyspnea in obese patients with HFpEF.[11]

Pericardiectomy and/or surgical removal of EAT would potentially relieve intrapericardial pressure. It is reasonable to consider that noticeable improvements in cardiac filling pressures and output could lead to evident benefits in symptoms and exercise performance. However, further studies are needed to demonstrate that this intervention and its intended effects can be achieved and maintained in HFpEF patients.[63]

Myocardial lipid infiltration. Patients with HFpEF also present higher concentrations of intramyocardial fat. This has been correlated with the severity of diastolic dysfunction, particularly in women compared with men.[39,64] However, whether myocardial lipid infiltration and accumulation of EAT are common bystander or one comes originally from the other, needs further investigation.

SOURCE OF PRO-INFLAMMATORY CYTOKINES AND DRIVER OF SYSTEMIC AND METABOLIC AND COMORBIDITIES. Metabolic and cardiovascular conditions such as obesity and diabetes (which typically coexist in HFpEF) are particularly associated with accumulation of visceral and epicardial adiposity and imbalances in adipocyte-associated cytokines. EAT, which in healthy conditions produces adiponectin and nurtures the myocardium, shifts its biology and becomes the source of several pro-inflammatory cytokines (leptin, tumor necrosis factor-alpha, interleukin (IL)-1B and IL-6, and resistin). Given its close proximity, EAT secretome is expected to be readily transmitted to the underlying myocardium. This can be made via: 1) vasa vasorum; 2) paracrine function and, as recently described; or 3) extracellular vesicles (EVs)[28] (**Figure 4**). EVs are membrane-bound particles, mostly implicated in obesity-related diseases, that store adipokines and travel to local or distant targets triggering different biological functions.[28]

FIGURE 4 Regional Implications of Epicardial Adipose Tissue



A systemic inflammatory signal produces an imbalance in adipocyte-associated pro-inflammatory cytokines; due to the anatomical proximity, epicardial adipose tissue (EAT) secretome can reach the myocardium directly via vasa vasorum and paracrine pathways, and transduce the systemic inflammatory stimulus to the underlying myocardium. Due to the regional implications of EAT, if these process affects the atria, the pro-inflammatory mechanisms could lead to atrial fibrillation. These mechanisms in the left ventricle trigger distensibility and filling pressures changes that might have a role in heart failure.

In particular, EVs originated in the EAT, have a distinctive pro-inflammatory, profibrotic, and pro-arrhythmic profile.[28]

Inflammation. These same comorbidities that are associated with higher visceral and epicardial adiposity also activate the Nod-like receptor family pyrin domain containing 3 (NLRP3 inflammasome). Inflammasomes are multimeric protein complexes, serving as intracellular factor sensors that regulate inflammatory responses and pyroptotic cell death.[65,66] NLRP3 inflammasome is involved in the pathogenesis of cardiovascular diseases, ranging from atherosclerosis to acute myocardial infarction, HF and AF. In the epicardium, NLRP3 inflammasome transforms epicardial cells into a powerhouse for the production and release of pro-inflammatory cytokines (especially those belonging to the IL-1 family). At the same time, IL-1 also triggers NLRP3, leading to the production of more cytokines.[67] Targeting the NLRP3 has been suggested as a novel anti-AF approach to prevent from both electrical and structural remodeling. Pharmacological inhibition of IL-1β, transcriptional/post-translational modifications of NLRP3, the use of several antibodies and even colchicine are potential new strategies under investigation to target inflammasome signaling[65,66,68]

Other markers of inflammation have been found to be increased in EAT, especially in patients with HF, such as α1-antichymotrypsin (also known as serpin A3) or TP53 (which is inversely correlated with the beneficial adiponectin).[34,61] Epicardial-released adipokines may also induce angiogenesis by releasing several angiogenic factors (vascular endothelial growth factor and thrombospondin-2) and several matrix metalloproteinases.

Specific markers of adipocyte inflammation in the epicardium, such as FABP4[69] can predict outcomes better than EAT volume alone. FABP4 (which is highly expressed in EAT in inflammatory states and co-regulated with leptine)[33] enhances neutrophils recruitment and oxidative stress in macrophages, thus contributing to structural heart disease and cardiac contractile dysfunction. FABP4 levels are associated with myocardial mass in patients with obesity and HF.[33,69-71]

Fibrosis. Epicardial-released adipokines may induce oxidative stress and myocardial fibrosis.[72,73] EAT produces activin A, visfatin, transforming growth factor-β1, and monocyte chemoattractant protein-1, which have been associated with fibroblast proliferation, collagen synthesis, and myofibroblast activation (and therefore with atrial and ventricular fibrosis). Expansion and inflammation of EAT also promote the synthesis of leptin, tumor necrosis factor-alpha, IL-1B, IL-6, and resistin. Leptin has drawn special attention by its effects on calcium

handling, collagen I production by cardiac myofibroblasts, and sodium reabsorption in the renal tubules[74,75] (which combined contribute to cardiac fibrosis). Circulating leptin is elevated in patients with obesity, HFrEF, and HFpEF[75] and it is correlated with the size of the epicardial adipocytes.[70,72,73,76] Resistin favors the infiltration of macrophages, destroys neighboring microvascular systems, and activates profibrotic pathways.

Pro-arrhythmic effect. Regional accumulation of EAT induces structural and electrical remodeling of both ventricles and atria.[34,61] EAT is mostly located in the posterior wall around the pulmonary veins, which is a source of triggers, and within the atrial anterior wall, roof and floor, as well as in the mitral isthmus, which are frequent targets for catheter ablation.[50]

In patients with AF, direct modification of EAT (for example, with that obtained with the epicardial left atrial appendage occlusion) seems to imply more benefits compared with the endocardial occlusion: more reductions in adrenaline and aldosterone and greater increases in adiponectine, which would traduce in less activation of the sympathetic and renin-angiotensin system.[77] The stimulation of autonomic nerves of EAT can shorten the action potential, increase Ca2+ release, reduce atrial conduction velocity, and increase the heterogeneity of conduction. Botulinum toxin may block parasympathetic nerves to release acetylcholine,[78-80] and it has been shown that botulinum toxin injections into EAT decrease the incidence of atrial arrhythmias and the burden of AF in patients with AF during a 3-year follow-up.[78-80]

SGLT2i, GLP-1RA, AND EAT

Newer therapies that reduce the risk of several cardiovascular disorders, including HFpEF, have also demonstrated to exert parallel effects modifying the volume and biology of EAT.[20,21,81] At the same time, most of the antidiabetic drugs that have been associated with worsening HF are associated with increased adipogenesis, accumulation of EAT, and fluid retention.[82] Sulfonylureas (which are insulin secretagogues) enhance secretion of pro-inflammatory adipokines that some have suggested to increase the risk of HF.[82] Earlier clinical trials with thiazolidinediones have consistently demonstrated an increased risk of HF.[21] This detrimental effect could be related to a potentiation of the action of insulin, which enhances sodium reabsorption in the kidney and activates lipogenesis in adipose tissues, especially in the epicardium.[22] Patients treated with insulin have higher EAT thickness,[82,83] increased sodium and water retention, and elevated risk of death and HF hospitalization, even after adjusting for other predictors of adverse outcomes.[21,84]

In contrast, EAT responds to newer antidiabetic therapies that have demonstrated early and clinically meaningful reductions in major cardiovascular outcomes:

Sodium-glucose co-transporter 2 inhibitors (SGLT2i) are the first drugs reducing the risk of cardiovascular death or HF hospitalizations in large-scale definitively powered trials in HFpEF.[85-88] The ability of these drugs to decrease myocardial inflammation and fibrosis, and to improve microvascular function and ventricular hemodynamics could be explained by a preferential modulation of EAT.[89] SGLT2i may also increase diuresis and mitigate the development of cardiac fibrosis via reduction of the activity of sodium-hydrogen exchangers in the kidney and in the heart.

Both glucagon-like peptide (GLP)-1a and SGLT2i have demonstrated to reduce EAT.[90-93] The EMPATROPISM clinical trial is the only study that has specifically addressed changes in EAT in patients with HF (**Table 1**). Reduction in EAT is likely associated with the reduction in overall adiposity and may be explained, in part, by the hypoglycemic activity of SGLT2i and GLP-1Ra. However, other unknown mechanisms might be involved, since it has been shown that in patients with stage 3 chronic kidney disease, in whom the pharmacodynamic activity of SGLT2i is reduced and thus blood glucose levels not well controlled, SGLT2i can also decrease blood pressure and body weight.[101]

Selective visceral fat reduction, instead of overall adiposity, has been recently suggested as a key factor in the metabolic improvement that follows a weight loss.[7] As recently discovered, the presence of GLP-1, GLP-2,[102] and SGLT2 receptors[90] in EAT suggests a direct-acting effect upon this adipose deposit. GLP-1R expression is associated with upregulated genes involved in FFA oxidation, white-to-brown adipocyte differentiation, and decreased adipogenesis. SGLT2 protein expression and functional activity are increased in HF, diabetes, and certain metabolic disorders.[91] Therefore, direct target of GLP-1 receptors in EAT implies a potential strategy to the reverse metabolic derangement, reducing local adipogenesis, improving fat utilization, and inducing brown fat differentiation.[30] Dapagliflozin, an SGLT2i, has shown to improve the differentiation of EAT cells, reduce its secretion of pro-inflammatory cytokines, and increase glucose uptake independently of insulin resistance.[101]

Both pharmacological groups (SGLT2i and GLP-1Ra) have seen expanded clinical recommendations,

TABLE 1 Effects of GLP-1 Agonists, Statins, and SGLT2 Inhibitors on Epicardial Adipose Tissue

Treatment Group	First Author	Weeks	Patients	n	Treatment	EAT Change (%)	Imaging Technique	Measurement
GLP-1 agonists	Iacobellis et al[94]	24	T2DM and obesity	95	Liraglutide vs control	−42	Echocardiography	Thickness
	Morano et al[95]	18	T2DM	27	Liraglutide or exenatide (pooled together)	−13	Echocardiography	Thickness
	Iacobellis et al[96]	12	T2DM and obesity	30	Semaglutide	−20	Echocardiography	Thickness
				30	Dulaglutide	−20		
	Lit et al[97]	12	T2DM and obesity	21	Liraglutide	−29	CMR	Thickness
Statins	Park et al[98]	24	CAD	82	Atorvastatin	−10	Echocardiography	Thickness
				63	Simvastatin + ezetimibe	−3		
	Alexopoulos et al[99]	48	Hyperlipidemic postmenopausal women	194	Atorvastatin	−3	CT (images used for calcium score)	Volume (semiautomatic analyses)
		48		296	Pravastatin	−0.8[a]		
SGLT2 inhibitors	Iacobellis et al[93]	24	T2DM and CAD	40	Dapagliflozin vs control	−20	CT	Volume (semiautomatic analyses)
	Yagi et al[92]	24	T2DM	13	Canagliflozin	−20	Echocardiography	Thickness
	Fukuda et al[90]	12	T2DM	9	Ipragliflozin	−12	CMR	Volume (semiautomatic analyses)
	Bouchi et al[91]	12	T2DM and obesity	19	Luseogliflozin	−5	CMR	Volume (semiautomatic analyses)
	Requena-Ibáñez et al[100]	24	Non-T2DM, HFrEF	33	Empagliflozin vs placebo	−10	CMR	Volume (manual tracing)

In the study from Requena-Ibáñez et al[100], empagliflozin is associated with significant reductions in EAT volume (−5.14 mL; 95% CI: −8.36 to −1.92) compared with placebo (−0.75 mL; 95% CI: −3.57 to 2.06; $P < 0.05$). [a]Nonsignificant.

CAD = coronary artery disease; CMR = cardiac magnetic resonance; CT = computed tomography; EAT = epicardial adipose tissue; HFrEF = heart failure with reduced ejection fraction; GLP = glucagon-like peptide; SGLT2 = sodium-glucose co-transporter 2; T2DM = type 2 diabetes mellitus.

however, guidelines do not specify between patients at risk of HF and individuals with manifest HF, or those with different HF phenotypes.[83] Based on existing evidence, the cardiovascular effect of GLP-1 and SGLT2i would be different. SGLT2i have consistently demonstrated a reduction in the risk of HF hospitalization regardless of baseline cardiovascular risk or history of HF. These benefits are also observed in patients with and without diabetes and across a wide range of EF. On the other hand, GLP-1 Ras have an overall neutral effect on HF outcomes, albeit to a varying degree for individual drugs, and even with uncertainty about safety in patients with HFrEF.[21] In patients with HFpEF, no studies to date have specifically investigated the potential benefit of GLP-1 Ras.[83]

SGLT2 INHIBITORS REDUCE EAT REGARDLESS OF OBESITY PARADOX. Obese people are at markedly increased risk of HF (especially HFpEF, but also HFrEF). However, an obesity paradox has been reported in many individual trials and large meta-analyses[103]: obese patients with HF seem to have a better prognosis compared with their nonobese counterparts. Furthermore, weight loss in obese HF patients is usually associated with disease progression.[104,105] Nonetheless, there seems to be 2 exceptions where weight loss does not imply worsening HF: 1) physical activity; and 2) treatment with SGLT2i.

Recent evidence indicates that weight-loss programs, as well as programs increasing physical activity, are associated with increases in stroke volume and with reductions of clinical events.[106] Supervised endurance training and bariatric surgery also reduce EAT in overweight and obese patients.[74]

SGLT2i have demonstrated to reduce body weight, adiposity, and at the same time provide cardiovascular benefit in both HFpEF and HFrEF. In large-scale clinical trials, empagliflozin and dapagliflozin improve outcomes across the spectrum of EF.[85,88,107] and it has been recently demonstrated a consistent benefit in HF patients across different body mass index categories.[104,105] In mechanistic studies, there is evidence of structural and functional benefit decreasing EAT volume and weight in HFrEF with empagliflozin.[100] In the EMPATROPISM clinical trial, empagliflozin was associated with reduced EAT volume and body weight but, most importantly, with reverse myocardial remodeling and improvements in pro-inflammatory biomarkers.[100] It has been recently demonstrated that in type 2 diabetic patients with normal LV function, empagliflozin does not improve LV global longitudinal strain or exercise tolerance;

however, when subclinical dysfunction is present (longitudinal global strain <16.5%), it can improve LV contractility.[108]

It has been postulated that SGLT2i mimic the molecular beneficial effects of caloric restriction. Some of these effects are linked with the activation of sirtuin, which is induced by nutrient deprivation and mediates the ability of caloric restriction to protect organ function. Sirtuin activation has been associated with cardiovascular benefits in patients without HF and preclinical models of HF.[72]

FUTURE PERSPECTIVES

HFpEF is increasing exponentially and there is an imperative need to understand the structural and functional impact of adiposity and, most importantly, to develop effective tailored therapies. Some considerations should be taken for in vivo future clinical research:

1. EAT should be adequately recognized. Most of the studies focusing on AF do not always distinguish between epicardial (below the pericardium) and paracardial adipose tissue (outside the pericardium, mediastinal or intrathoracic).[59] Nomenclature has not been consistently used, thus leading to misconceptions. As it has been described in this review, embryologically, anatomically, and biochemically EAT is a very distinct fat deposit.
2. The anatomical distribution of EAT along the heart is not homogeneous. Therefore, 3-dimensional assessment (volume) is more reliable in order to estimate anatomic location and total EAT burden. In fact, dynamic changes in EAT, as those observed in clinical trials or experimental studies, can potentially be missed using 1- or 2-dimensional assessment (thickness, diameter or areas).[36]
3. EAT should not be considered as a whole entity.[52] Periatrial, periventricular, and pericoronary EAT have specific transcriptomic signature and different influence on neighboring cardiac structures. Accordingly, a different functional implication is expected with different EAT compartments. Future studies addressing these differences are warranted.
4. Future research should ideally tailor investigations to evaluate the effect of GLP-1 Ras in HFpEF and HF patients across the EF spectrum. A better understanding of the specific underlying mechanisms would help narrow down groups of cardiovascular patients who may respond to further personalized treatment.

CONCLUSIONS

HFpEF encompasses a broad range of metabolic, inflammatory, and adipogenic comorbidities. Expansion and inflammation of the EAT may act as a transducer to driving the biological derangements of the systemic disorders into ventricles and atria. EAT accumulation induces myocardial fibrosis, microvascular rarefaction, and upregulation of local and systemic fibrosis that could be mechanistically associated with AF and HF. New antidiabetic drugs, SGLT2i and GLP-1R agonists have shown to directly affect EAT, reducing the secretion of pro-inflammatory molecules and improving glucose homeostasis. A potential new role of EAT as a therapeutic target is expected, however, further investigation will define the pathophysiological cause-effect relation between the transformation and increase of EAT and the subsequent new onset and progression of HFpEF.

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