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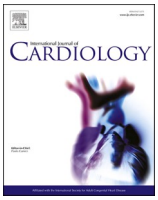

Pericardium, epicardial adipose tissue, and heart failure with preserved ejection fraction: Pathophysiology, quantification and treatment target[1]

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ABSTRACT

Heart failure is an important cause of mortality and morbidity worldwide. Heart failure with preserved ejection fraction (HFpEF) incidence and prevalence is increasing, and the phenotype associated with obesity is the most frequent. Epicardial adipose tissue (EAT) is directly associated with systemic obesity and several previous studies have shown a clear link between EAT and HFpEF. Moreover, the restriction induced by the pericardium is also linked to HFpEF. In this review we will describe the epidemiological association between the pericardium, EAT and HFpEF, how to quantify EAT, what are the pathophysiological mechanism to explain theses association and how can the pericardium and EAT be a treatment target in patients with HFpEF.

1. Introduction

Recent estimates from the 2019 Global Burden of Disease Study, indicate that approximately 56 million people worldwide have a heart failure (HF) diagnosis, that is a leading cause of disability and death [1]. Ischemic and hypertensive heart disease are the main causes of HF in males and females, respectively [2]. Between 1990 and 2019, there was an increase in HF cases (particularly in younger patients), but a slight decrease in age-standardized rate in both genders [2,3]. In developed countries, the prevalence of known HF is generally estimated at 1% to 2% of the general adult population [3]. However, echocardiographic screening studies point to a prevalence of around 4.2%, a figure that might be a more realistic estimate, compared to data based on registries containing only established cases [3]. In fact, epidemiologic studies on HF have some limitations, due to differences in definitions and population, and also because most studies rely on administrative data, that usually lack important clinical information, or in hospital records, which cannot capture patients receiving care in outpatient settings.

HF presents in two major phenotypes – HF with reduced ejection fraction (HFrEF) and HF with preserved ejection fraction (HFpEF), with an additional phenotype with mildly reduced ejection fraction (HFmrEF). Despite similar clinical presentation, the mechanisms that lead to HFrEF and HFpEF are distinct [4]. A fact that supports this observation is that the neurohormonal therapies that are the cornerstone in the treatment of HFrEF have failed to prove unequivocally its benefit in HFpEF patients. Data from the ESC Heart Failure Long-Term Registry showed that overall, 59.8% of HF patients were classified as having HFrEF, 24.2% as having HFmrEF and 16.0% as having HFpEF [5]. Patients with HFpEF are older, predominantly females, with overweight / obesity and other comorbidities, such as hypertension, diabetes, and atrial fibrillation, that may mimic HF symptoms and can cause some HFpEF misdiagnosis [5,6]. Nevertheless, there is a clear transition towards an increase in the prevalence of HFpEF while the prevalence of HFrEF seems to be stable or even declining [7]. In the Swedish HF Registry, the overall proportion of HFrEF in 2000–2004 versus 2013–2016 decreased (60% to 49%) whereas the overall proportion of HFpEF increased (20% to 30%) [7].

The increase in incidence and prevalence of HF worldwide, follows a concomitant increase in the prevalence of obesity. HFpEF is very heterogeneous, and it is not a disease per se, but rather a clinical syndrome associated with several comorbidities [6]. It is important to stratify this entity into pathophysiological homogenous subtypes to facilitate phenotype-specific treatments. Specific HFpEF phenotypes emerge from different predisposing conditions that will determine different treatment strategies. These phenotypes are the cardiorenal, autoimmune / inflammatory and cardiometabolic, being the cardiometabolic phenotype the most prevalent, mainly driven by obesity, metabolic syndrome, and type 2 diabetes [4].

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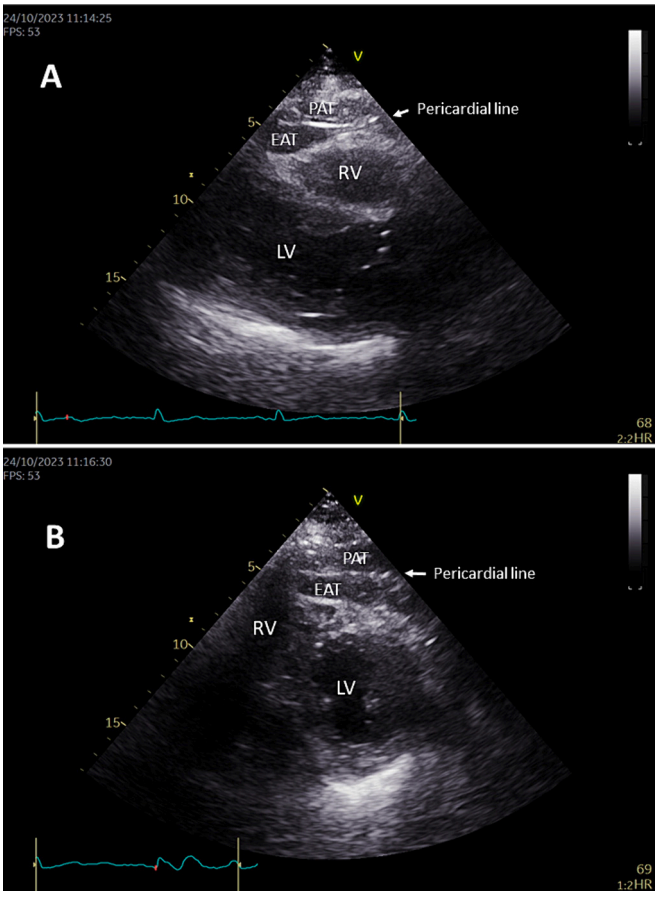

Fig. 1. Quantification of the Epicardial Adipose Tissue by Echocardiography. Images were obtained from the left-parasternal acoustic window in long-axis (A) and short-axis (B). Epicardial thickness can be measured in any of those windows. Pericardium line is detected and epicardial and paracardial adipose tissue can be distinguished. EAT – epicardial adipose tissue; PAD – paracardial adipose tissue; LV – left ventricle; RV – right ventricle.

Adipose tissue is classified in two functionally distinct types. White adipose tissue, the predominant type of fat, is primarily involved in fat / energy storage (high fatty acid uptake), and it releases several adipokines and cytokines, with paracrine and endocrine effects, regulating the body metabolism [8]. Moreover, it also protects the organs from mechanical and thermal damage. It can be subclassified into visceral and subcutaneous [4,8]. As total body fat increases, there is saturation of fat storage depots in the subcutaneous tissues and accumulation in alternative fat depots, such as the viscera and epicardial space [9]. The pathophysiological mechanism underlying the shift from subcutaneous to ectopic fat deposition have not been clearly elucidated yet [10]. Men usually have more visceral adipose tissue (VAT) and women more subcutaneous adipose tissue [4,11,12]. However, in older individuals, this sex influence is no longer present [4,11,12]. Brown adipose tissue have adipocytes that are smaller and multilocular (with several lipid droplets) and rich in mitochondria, expressing Uncouplig Protein 1, that stimulates the process of non-shivering thermogenesis [8]. It dissipates energy from fatty acids to generate heat [8].

Epicardial adipose tissue (EAT) exhibits embryological and morphological similarities with VAT, both deriving from splachnopleuric mesoderm [10]. Systemic effects have been predominately reported for VAT, intra-hepatic and intramuscular fat [10]. Prevalent local activity was instead recognized in the kidney and heart fat, although they are a true form of VAT [10]. EAT is poorly correlated with subcutaneous fat volume, and moderately correlated with abdominal visceral fat volume [10]. VAT has a strong correlation to HFpEF development, hospitalization, and mortality, which is probably associated with increased insulin resistance / diabetes, decreased arterial compliance / arterial hypertension, and systemic endothelial dysfunction and inflammation, particularly in women [4]. EAT is also correlated with metabolic syndrome components [10]. However, the strength of the association is less than one-half of that of VAT, supporting a more local effect instead of systemic [10].

Prospective studies in large, community-based cohorts of patients without cardiovascular diseases, showed that higher pericardial fat volume (PFV) is associated with a linear increase in the risk of HF in both men and women [11]. Although the amount of PFV was lower in women, the relative risk of de novo HF was higher in women, compared to men [11]. In fact, higher PFV doubled the risk of HF in women but in men, the risk was only 53% higher [11]. The proportion of cases of HF attributable to high PFV was 32% in women and 13% in men [11]. This association was very strong with HFpEF and modest with HFmrEF. No association was observed with HFrEF [11]. Moreover, an association between EAT and HF is still present, even in fully adjusted models with abdominal visceral fat volume as an additional covariate [10].

2. Epicardial adipose tissue assessment and quantification by imaging techniques

Epicardial adipose tissue (EAT) is the fat deposit located directly between the visceral layer of the pericardium and the myocardium [9,11]. This VAT is mainly distributed around coronary arteries, atrioventricular and interventricular grooves, and right ventricle (RV) [9,11]. Approximately 75% of epicardial fat lies over the RV [8,10]. In non-obese individuals, EAT covers 80% of the heart's surface and it accounts for approximately 20% of total heart's weight [8,10]. In addition to EAT, the heart muscle is surrounded by the paracardial adipose tissue, which lies between the pericardium layers and on the external surface of parietal pericardium [9,11]. There are multiple imaging methods to measure EAT. Depending on the techniques, it is possible to measure its thickness or volume.

Transthoracic echocardiography allows the visualization and measurement of the EAT thickness [13]. EAT can be identified as the echo-free space between the outer wall of the myocardium and the visceral layer of pericardium but EAT can also appear as an echo-dense space in cases of inflammation or large amounts of EAT (Fig. 1) [14]. EAT thickness is measured at end-systole, perpendicularly to the RV free wall [14]. The use of parasternal long and short-axis views allows the most accurate measurement of EAT on the RV, and this point is recognized as the highest absolute epicardial fat layer thickness [15]. Although echocardiography has several advantages, such as low cost, accessibility, and reproducibility, it cannot give an adequate view of all cardiac segments and is highly dependent of acoustic windows [16]. Nonetheless, echocardiography measurements of EAT over the free wall of the RV correlate well with cardiac magnetic resonance (CMR) and is frequently used in clinical research on this topic [15].

Cardiac computer tomography (CCT) allows the measurement of EAT volume, besides thickness. It provides additional functional information by being able to measure regional EAT and to assess its density using Hounsfield units [17]. Other advantages are submillimeter collimation, high temporal and spatial resolution and three-dimensional views of the heart and its epicardial surface [16]. Owing to this, CCT is currently the preferred method to determine EAT over other imaging modalities. There are various software programs that offer a simple semi-automated approach for quantification of EAT, with high reproducibility, that depends on the CT attenuation thresholds used to define adipose tissue (Supplemental Fig. 1) [18]. However, CT attenuation differences of EAT may exist in the presence of iodinated contrast and inflammation. Depending on the software, for the measurement of volumes of EAT, fibrous pericardium should be manually traced, on axial planes, from the pulmonary artery bifurcation to the diaphragm, following by assignment of the attenuation threshold from −30 to −190

Hounsfield units (HU) to fat. Afterwards, EAT is detected, and using three-dimensional reconstruction, volume is automatically calculated by the software and presented in cm^3 [18]. A recent study by Liu et al., showed that in patients with HFpEF who underwent non-contrast CCT, EAT density is inversely correlated with EAT volume, as well as with all cardiometabolic risk factors [19]. They also showed that EAT density ≤ -76.0 HU can better identify the presence of more severe metabolic syndrome. Moreover, it was also shown that patients with lower EAT density ($\leq$ 76.2 HU) have higher cumulative incidence of all-cause mortality and heart failure readmissions, suggesting a potential prognostic role. It is however uncertain whether the decrease in attenuation in HFpEF patients is caused by adipocyte hyperthrophy, increased interstitial fibrosis or reduced capillary density. It might represent expansion of white adipose tissue, which is denser, larger and secretes more inflammatory factors compared to brown adipose tissue [19].

Similarly to CCT, CMR is also able to provide volumetric measurement of EAT, beside its thickness, and can measure regional EAT locations. If associated with H-magnetic resonance spectroscopy techniques, CMR provides additional information regarding intramyocardial lipid content (Supplemental Fig. 2). Compared with CCT, CMR has lower spatial resolution but it has excellent soft tissue contrast, making it possible to separate EAT from the different fat layers surrounding the heart [14,17]. Depending on the software, for the measurement of volumes of EAT on CMR, the outer wall of the myocardium and the visceral pericardium should be manually delineated on consecutive end-diastolic short-axis slices covering the entire left and RV from base to apex. Then, EAT is obtained after the summation of data from all slices and volume is automatically calculated by the software and presented in cm^3 [20].

3. Pathophysiology of the pericardial and epicardial adipose tissue in HFpEF

EAT lies directly over the myocardial surface, with no separating fascial plane, without any anatomical boundary, facilitating higher adipocyte – myocyte interaction [8,10,21]. Furthermore, its blood supply comes directly from branches of coronary arteries, establishing a common microcirculation that enables a direct interplay with the myocardium through paracrine or vasocrine mechanisms [9,10]. Paracardial adipose tissue comprises both the adipose tissue surrounding the heart cavities but also perivascular adipose tissue and is supplied by non-coronary arteries [22].

Under healthy conditions and given its spatial location, EAT has an important function of mechanical protection for nearby coronary arteries, shielding them from tension, twist and compression induced by the arterial pulse wave and myocardial contraction [8,10]. EAT has also a pivotal role as a local energy supplier to the myocardium, primarily utilizing free fatty acids (FFA) stored as triglycerides for energy production, during periods of elevated energy requirements, satisfying the high energy demands of the heart [8,10]. Moreover, this rapid utilization of FFA serves as an additional protective mechanism, shielding the myocardium from potential cardiotoxic effects associated with excessive FFA exposure [8,10]. As a metabolic active tissue, EAT secretes adipokines and cytokines that interact with adjacent myocardium through the shared microcirculation. Adiponectin emerges as the most important adipocyte-derived adipokine, improving endothelial function and reducing oxidative stress, as well as the levels of interleukin (IL)-6 and C-reactive protein [8,10,23]. Adrenomedullin is another important protective adipokine [8,10,23]. In addition, secretion of omentin can improve endothelial function by stimulating endothelial nitric oxide synthase [8,10,23]. These protective effects of EAT to the nearby myocardium and vessels contributes to its anti-inflammatory, anti-atherogenic, anti-apoptotic, and fibrosis-reducing properties [8,10,23].

Despite all these protective effects in healthy conditions, EAT function can be disrupted by adverse metabolic and inflammatory conditions [24]. The change from a physiological to pathological phenotype of EAT is still not well understood, but it is possibly influenced by intrinsic and extrinsic factors. In obesity, as epicardial fat accumulates, it changes its biological characteristics, with a shift in adipokine synthesis: decrease in adiponectin and increased synthesis of proinflammatory adipokines, such as leptin, resistin, tumor necrosis factor-α (TNF-α), IL-1β, −6, −8, −10, monocyte chemo-attractive protein 1 (MCP-1), plasminogen activator inhibitor 1 (PAI-1), and all of them will exert a deleterious effect [8,10,21,25]. One mechanism to explain this shift is the concept of adipose tissue hypoxia [24]. As adipose tissue accumulates, the microcirculation rarefaction reduces oxygen delivery and induces local hypoxia. This prompts adipocytes to release pro-inflammatory cytokines, attracting macrophages and other immune cells and a downregulation of adiponectin production [26,27]. This proinflammatory state induces a deleterious positive feedback cycle, as EAT continues to produce more proinflammatory adipokines that further recruit immune cells [8,10]. The infiltrative-lipotoxic hypothesis, suggests that this inflammatory infiltration of the EAT, diffuses and infiltrates directly the myocardium and surrounding blood vessels via a paracrine pathway, secreting deleterious adipokines [28]. Moreover, mesenchymal stem cells derived from the epicardium can migrate to the myocardium and transform into fibroblasts [21]. In addition, there is also intracellular accumulation of fat (myocardial steatosis) or extension between myocardial bundles and muscle fibers (extracellular infiltration of fat) [11,12]. All these mechanisms will promote abnormalities of the microcirculation and activate pro-fibrotic pathways inducing arterial stiffness, endothelial dysfunction, structural and electric remodeling of cardiac myocytes, myocyte hypertrophy, fibrosis, and stiffness, all of which play a role in HFpEF pathogenesis [4,29]. Furthermore, by a vasocrine mechanistic pathway, proinflammatory adipokines are released in the vasa vasorum, exerting mainly local effects. They can also be carried out downstream provoking systemic deleterious effects, such as those associated with metabolic syndrome components [30]. The release in the general circulation may contribute to the systemic inflammatory state, which in turn promotes the accumulation of more EAT, thereby creating a positive feedback loop [21].

Moreover, leptine stimulates the secretion of aldosterone and angiotensin II and increase in neprilysin with increasing sodium retention and volume expansion [4]. Therefore, the hypothesis of a leptin-aldosterone-neprilysin axis has been recently suggested as an additional pathway linking EAT dysfunction to the development of HF, alongside with the suppression of thermogenic genes, such as peroxisome proliferation-activated receptor gama (PPAR-γ) [10].

EAT has also been linked to a higher recurrence risk after catheter ablation in atrial fibrillation patients [31]. Moreover, it has also been shown that EAT (particularly atrial) is associated with subclinical incident atrial fibrillation, detected by continuous monitoring in patients without a previous history of atrial fibrillation, with an increase in risk up to 3-fold [32]. This is particularly relevant because atrial fibrillation is very prevalent in HFpEF patients, and it is an important cause for heart failure decompensation episodes. Mechanisms are not fully understood, but potentially, it can be explained by atrial myocardial fatty infiltration, as well as paracrine-associated myocardial fibrosis and inflammation [31].

Another important mechanism that contributes to HFpEF is the direct mechanical compression and restraint resulting from the accumulation of EAT in the pericardium. Ventricular filling is restrained by the pericardium. Left ventricular (LV) end-diastolic pressure (EDP) varies directly with left ventricular end-diastolic volume (LVEDV) up to a certain point [33]. With additional increases in venous return, LVEDP will increase sharply, and this is related to pericardial restrain and not by viscoelastic muscle properties [33]. It is estimated that 20% to 40% of LVEDP is related to this extrinsic restraint [33]. Moreover, acute increases in RV volume, together with pericardial restrain will shift the left ventricular (LV) pressure – volume curve upward, due to the diastolic ventricular interaction [33]. Any increase in pericardial restraint augments this parallel interaction between the RV and LV[33]. Therefore, any increase in right heart volume will cause a corresponding decrease in left

heart volume or an increase in left heart pressure to maintain its volume [33]. It is then possible to develop lung congestion even with an underfilled LV due to low transmural pressure when right-heart and pericardial pressure are very high [33]. Possible causes for an increase in pericardial restraint are an enlargement in heart volume (such as in the case of hypertrophy), alterations of the viscoelastic properties of the pericardium (e.g., by radiation, aging, or inflammation), or by accumulation of pericardial fluid or epicardial fat [33].

In the obesity HFpEF phenotype, pericardial restraint has an important role, because this increase in EAT will cause greater pericardial restraint and ventricular interdependence due to a direct mechanical effect due to compression of EAT on the myocardium within a close pericardium sac [9]. This is associated with worse peak aerobic capacity, higher biventricular filling pressures and higher pulmonary pressures at rest and during exercise [9]. EAT has an asymmetrical distribution and most of it is located around the RV, which can explain the fact that these deleterious effects are more pronounced in the RV [12]. Increased EAT alongside the RV is associated with an increase in RVEDP, independently of RV afterload and obesity, which is associated with lower peak workload and peak oxygen uptake in cardiopulmonary exercise testing, that is, a reduction in exercise capacity [12]. Furthermore, obesity is associated with an increase in circulating plasma volume, which in turn leads to higher venous return to the right heart [9]. When cardiac filling is restrained by the pericardium, the RV is not able to dilate further in response to increase in venous return, and this will lead to enhanced ventricular interdependence [9]. At that point, the capacity of the LV to dilate in response to an increase in blood volume is impaired, and even modest increases in volume load, leads to cardiac overfilling and disproportionate increases in cardiac filling pressures [9,33].

4. New treatment targets for HFpEF

4.1. Targeting directly the pericardium and pericardial restraint

Animal experimentation showed that resection of pericardium, relieves pericardial restraint, and improves LV compliance, even with unchanged muscle properties [33]. Pericardiectomy increased LVEDV and improves Frank-Starling response, with improvements in stroke volume, cardiac output, and exercise capacity [33]. In humans, pericardiectomy performed in the context of cardiac surgery, increases LVEDV at similar filling pressures, just as it is observed in patients with congenital absence of the pericardium [33]. With exercise, the increase in right and left ventricular volume can be better accommodated, without significant increase in LV pressures [33].

Surgical therapies targeting pericardial restraint were recently tested. In a first in-human pilot study in four severely symptomatic (despite optimal medical therapy) obese female patients with HFpEF, a surgical antero-lateral pericardiectomy under direct thoracoscopic visualization through a left mini thoracotomy was tested [34]. This procedure improved central hemodynamics, avoiding the pathological increase in LV filling pressure during volume loading [34]. It also improved quality of life and peak oxygen uptake at 3 months, sustained at 6 months follow-up [34]. There were no adverse cardiovascular, renal, or cerebrovascular events during follow-up, although the first patient had to be re-admitted 14 days after the procedure due to a significant episode of inflammatory post-pericardiotomy syndrome [34]. The protocol was modified to administer colchicine to all patients before surgery and none of the remaining patients experienced this adverse event. Nevertheless, the small sample size, and the absence of a control group are important limitations of this pilot study. However, this is a hypothesis-generating study, that calls for future trials with less invasive, percutaneous pericardiectomy devices in the catheterization laboratory. This has been already tested in a porcine model of HFpEF, with a minimally invasive anterior pericardiotomy, performed percutaneously using a novel device and guided by fluoroscopy [35]. This treatment mitigated the increase in LV filling pressures in response to volume overload, and this effect was sustained at 4 weeks [35].

4.2. Targeting pericardial restraint independently of the pericardium

In the presence of pericardial restraint and ventricular interdependence, plasma volume can be reduced with diuretics, to reduce RV volume and improve LV filling [33]. Nitrates can also have the same effect by re-directing the blood volume to the systemic capacitance veins in the splanchnic and peripheral venous circulation [33]. In addition, any intervention that can reduce heart size (by hypertrophy regression or reverse remodeling) can also be helpful in reducing the effect of pericardial restraint. Therefore, the use of neurohormonal antagonists to achieve hypertrophy regression can also be a treatment alternative [33].

4.3. Targeting the epicardial adipose tissue

Any reduction of pericardial fat, either by weight loss, or by other means, can also reduce pericardial restraint [33]. Weight loss induced by low-calorie diet and exercise in moderately and severely obese individuals induces EAT reduction. A 12-week supervised aerobic exercise training program in obese middle-aged men, induced significant reductions in EAT, suggesting that this non-pharmacological strategy is effective [36]. In addition, bariatric surgery induces a massive weight loss, followed by a reduction in epicardial fat, the intensity of systemic inflammation, and a decrease in the risk of HF [21]. Two meta-analyses confirmed that targeting EAT with exercise, diet or bariatric surgery can all reduce cardiac adipose tissue volume [37,38]. This is also associated with improvements in cardiac hemodynamics, with reductions in right atrial pressure, pulmonary capillary wedge pressure and mean pulmonary artery pressure, including during exercise [37].

High doses of statins reduce EAT and decreases its proinflammatory characteristics, an effect that is independent of their lipid lowering effects [21]. This can explain the observed reduction in the risk of HF, assessed in patients without baseline HF, as well as a reduction in the risk of death in patients with HFpEF [21,39]. In patients with HFpEF, statins improve mortality rates, mainly by a reduction in sudden death and non-cardiovascular causes [37]. This was not observed in HFrEF patients [21,39]. Atorvastatin seems to induce a more significant reduction in EAT compared to simvastatin plus ezetimibe [40]. The beneficial effects might be obtained by their anti-inflammatory properties or by modulation of PPARs [41]. A deeper understanding of the underlying mechanisms is needed.

Sodium-glucose co-transporter 2 inhibitors (SGLT2i) reduce EAT and ameliorate its inflammation and secretion of deleterious adipokines. They also reduce myocardial fibrosis and improve ventricular diastolic filling dynamics [42]. Dapaglifozin, has been shown to increase glucose uptake, decrease the secretion of proinflammatory chemokines, and improve the differentiation of human EAT cells in-vitro studies, compared to insulin exposure [43]. In addition, in obese diabetic patients, treatment with dapaglifozin decreases EAT volume, assessed by computed tomography, as well as a reduction in PAI-1 and TNF-α secretion, suggesting that it can reduce the deleterious factors [43]. Compared to metformin monotherapy in obese diabetic type 2 patients, treatment with dapaglifozin induced a rapid and significant EAT reduction, independent of weight loss [44]. This might be one of the mechanisms, by which this class of drugs improve prognosis in the whole spectrum of HF phenotypes, including HFpEF.

Glucagon-like peptide 1 (GLP-1) agonists enhance the function of incretins and reduces EAT volume in obese individuals, stimulating browning and shifting the balance from obesogenesis to thermogenesis [8]. Liraglutide, a GLP-1 analogue, induces a substantial and rapid decrease of EAT [45]. Another study in obese type 2 diabetic patients, showed that a 12-week treatment with semaglutide or dulaglutide induced a rapid, sustained, and dose-dependent reduction in EAT thickness, compared to metformin [46]. However, in this study, they did

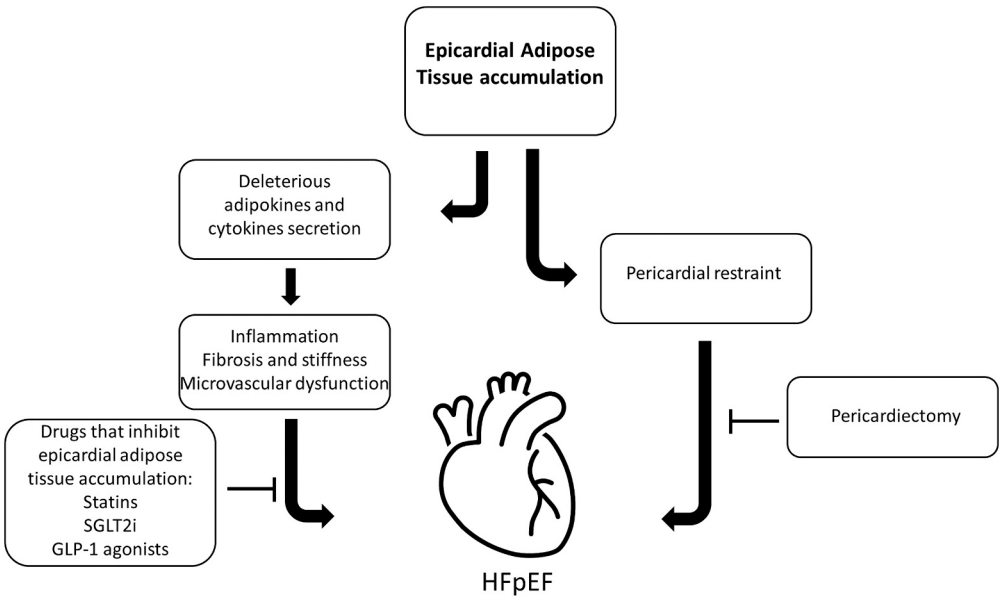

Fig. 2. Summary of the main mechanisms that link epicardial adipose tissue to heart failure with preserved ejection fraction and the treatment targets.

not improve its anti-inflammatory properties or its secretion of proinflammatory adipokines [46].

The recently published clinical trial STEP-HFpEF (Semaglutide in Patients with Heart Failure with Preserved Ejection Fraction and Obesity) studied the use of semaglutide in obese patients with HFpEF [47]. Compared to placebo, this treatment led to larger improvements in symptoms and physical limitations, exercise function, greater weight loss and greater reduction in C-reactive protein compared to placebo, without significant adverse events [47]. Therefore, this class of drugs is effective and safe for the treatment of obesity in HFpEF patients. The magnitude of benefit was directly related to the extent of weight loss. The study was not powered to assess clinical endpoints such as HF hospitalizations. Nevertheless, a reduction in the number of hospitalizations or urgent hospital visits for HF was noted. This evidence has just been strengthened by the recently published SELECT (Semaglutide and Cardiovascular Outcomes in Obesity without Diabetes) trial [48]. In patients with preexisting atherosclerotic cardiovascular disease and overweight or obesity but without diabetes, weekly subcutaneous semaglutide was superior to placebo in reducing the incidence of death from cardiovascular causes by 15%, nonfatal myocardial infarction by 28%, or nonfatal stroke by 7% at a mean follow-up of 40 months, although only non-fatal myocardial infarction reached statistical significance [48]. In addition, it also lowered the rates of HF events by 18% [48]. Although this was not a study in patients with HF, it suggests a significant effect on cardiovascular protection afforded by semaglutide. Additional clinical trials of semaglutide in patients with HFpEF are currently ongoing.

A recently published systematic review and meta-analysis analyzed the efficacy of cardiometabolic drugs (SGLT2i, GLP-1 agonists and statins) on reduction of epicardial adipose tissue [41]. All three drug classes showed a significant effect on EAT decrease [41]. However, for intensive high statin therapy, although significant, the effect on EAT reduction was rather mild, with a weighted average reduction of only 6% [41]. Regarding glucose-lowering drugs, GLP-1 agonists showed a two-times stronger effect on EAT reduction compared to SGLT2i. This effect was not only larger, but also more rapid and dose-dependent [41].

Hyperaldosteronism promotes the accumulation and inflammation of EAT and the development of microvascular rarefaction and fibrosis in the underlying cardiac muscle [49]. Therefore, the transformation of perivascular and epicardial fat to maladaptive proinflammatory phenotype may depend on mineralocorticoid receptor signaling [49]. Experimentally, blockade of mineralocorticoid receptors reduces oxidative stress, cardiac inflammation and fibroses [49]. It also enhances brown adipose tissue function and volume in humans [50]. Moreover, neprilysine inhibition augments the actions of endogenous peptides that not only have direct natriuretic effect, but also lower circulating levels of aldosterone and have important lipolytic and anti-inflammatory effects [49]. They can also inhibit cardiac fibrosis and promote capillary vasculogenesis [49]. However, the evidence to support the use of mineralocorticoid receptor antagonist and angiotensin receptor / neprilysin inhibitors with the objective of reducing or changing EAT are lacking.

5. Conclusions

There is a clear association between obesity and HFpEF. EAT is one of the mechanisms that explains this association. It can induce both a direct effect, through increased pericardial restraint, or an indirect effect, through the secretion of pathological adipokines to the adjacent myocardium. Treatment strategies directed to the increase in EAT in obese patients with HFpEF can improve symptoms and possibly prognosis and several studies are underway to demonstrate this possible treatment target (Fig. 2).

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CRediT authorship contribution statement

Ana Teresa Timóteo: Writing – review & editing, Writing – original draft, Conceptualization. **Francisco Barbas Albuquerque:** Writing – review & editing, Writing – original draft. **Bárbara Lacerda Teixeira:** Writing – review & editing, Writing – original draft.

Declaration of competing interest

None to declare.

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