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Epicardial Adipose Tissue and Heart Failure, Friend or Foe?

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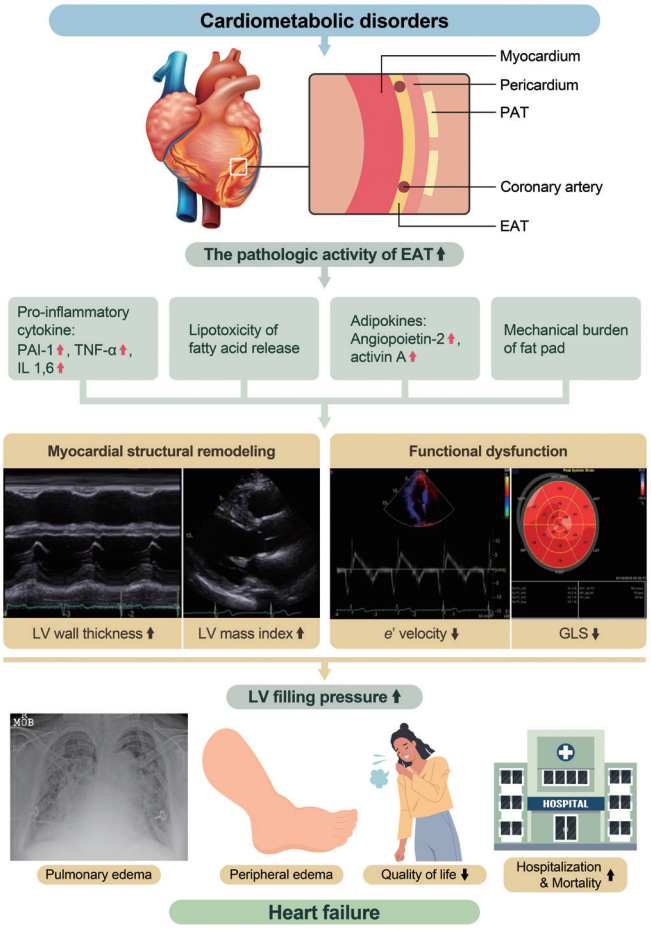

Highlights

- **EAT, easily assessed via imaging, is anatomically and functionally connected to the myocardium.**
- **Cytokines and fatty acids from EAT worsen myocardial remodeling, causing HF.**
- **In HFrEF, reduced EAT volume indicates metabolic dysfunction.**
- **Conversely, in HFpEF, higher EAT levels correlate with adverse hemodynamic profiles.**
- **EAT may serve as a target for HF therapies.**

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tion to direct lipid infiltration, EAT has been implicated in the development of myocardial dysfunction through the dysregulated secretion of adipokines. Experimental studies using EAT samples have shown that EAT secretes adipokines, such as angiopoietin-2 and activin A, which can induce cardiomyocyte contractile dysfunction and altered cytosolic calcium fluxes in a dose-dependent manner [47].

EAT is a large fat pad that surrounds the myocardium. This protects the coronary arteries within EAT against torsion. However, excessive amounts of EAT can cause a mechanical burden on the myocardium, leading to myocardial dysfunction. This negative relationship between EAT and myocardial function has been observed in elderly women, with a stronger association in the lateral e′ and s′ than in the septal e′ and s′ [48]. This supports the hypothesis that the mechanical burden of EAT induces myocardial dysfunction.

In addition to its mechanical effects, EAT also plays an important role in the pathogenesis of coronary atherosclerosis. EAT surrounds the epicardial coronary artery and shares microcirculation. Inflammatory cytokines, adipokines, and metabolic substrates secreted from EAT affect the pathogenesis of coronary atherosclerosis [49]. EAT is not equally distributed throughout the heart and tends to accumulate excessively at the focal site. Thus, EAT appears to be a transducer of metabolic disturbances and systemic inflammation in the underlying coronary artery [42]. In patients with suspected CAD, EAT thickness is independently associated with the presence of obstructive CAD and vasospasm, as confirmed by invasive angiography [50]. Moreover, studies using CT have demonstrated that an increased EAT volume is related to the vulnerable type of plaque, suggesting that EAT may contribute to the progression and vulnerability of coronary plaque [51]. Interestingly, EAT has also been implicated in coronary microvascular dysfunction, which plays an important role in the development of HF without obstructive CAD [52]. In patients without obstructive CAD, increased EAT volume is related to microvascular dysfunction, as evaluated using Rb-82 positron emission tomography [53]. These findings suggest that EAT is involved not only in the pathogenesis of epicardial CAD, but also in coronary microcirculation dysfunction. Fig. 3 summarizes the pathophysiologic mechanism of EAT.

EAT AND THE RISK OF HF

The association between the amount of EAT and myocardial dysfunction has been investigated in various clinical situations, including the general population, patients with metabolic disease without CVD, and patients with established CVD. We previously reported that a greater EAT thickness was correlated with a higher left ventricle (LV) mass index, worse LV systolic dysfunction represented by LV global longitudinal strain, and LV diastolic dysfunction in patients with suspected meta-

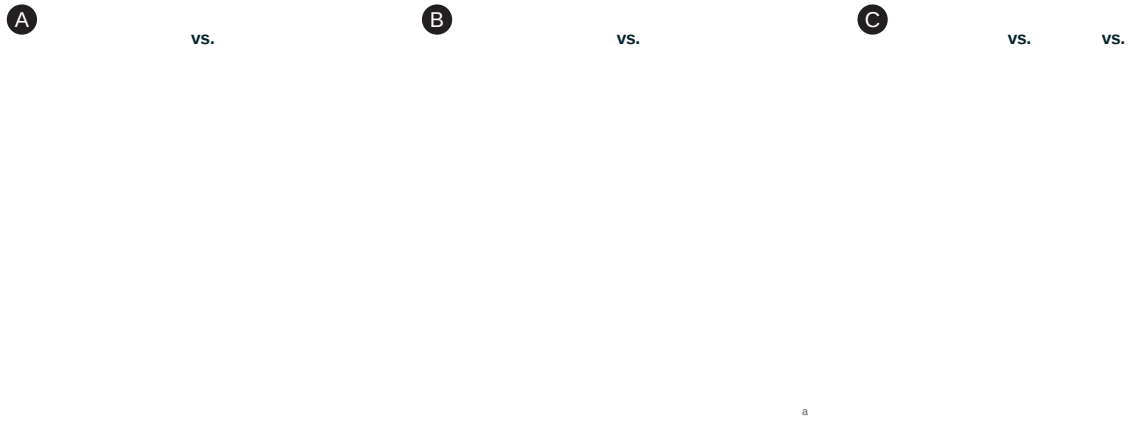

Fig. 4. The epicardial adipose tissue (EAT) amount in the heart failure with reduced ejection fraction (HFrEF), heart failure with preserved ejection fraction (HFpEF), and control groups. (A) EAT amount in HFrEF vs. control. (B) EAT amount in HFpEF vs. control. (C) EAT amount in HFrEF, HFpEF, and control. CMR, cardiac magnetic resonance. [a]This study used cm^3 as the measurement unit of EAT.

bolic syndrome and no overt CVD [1]. In elderly women without established CVD, an increase in the EAT amount was related to worse LV systolic and diastolic dysfunction [48]. In patients with acute myocardial infarction, EAT amount progressively increased according to the grade of LV diastolic dysfunction [54].

Excessive epicardial fat pad has an adverse effect on the myocardium. The amount of EAT varies according to the HF subtype: HF with reduced ejection fraction (HFrEF) or HFpEF. Fig. 4 shows the EAT amount in the HFrEF, HFpEF, and control groups. When patients with HFrEF and controls were compared, both cardiac MRI and echocardiography showed that the EAT amount was consistently reduced in patients with HFrEF than in controls [55-57]. However, the EAT amount in the HFpEF group was reported to increase in two studies and decrease in one study, when compared with that in the control group [58-60]. As the HFpEF study population was heterogeneous, this might have led to conflicting results. Few studies have compared patients with HFrEF and HFpEF with controls. In the study by Tromp et al. [61], which utilized both cardiac magnetic resonance (CMR) and echocardiography, it was observed that EAT thickness, as measured by echocardiography, was lower in HFrEF compared to the control group. However, EAT mass, as determined by CMR, was higher in the HFrEF group. It's worth noting that the method of measuring EAT can significantly influence the study's findings. Echocardiography primarily assesses EAT thickness at the RV free wall, whereas CMR provides a more comprehensive evaluation of EAT mass across the entire heart. Given that EAT covers a larger portion of the heart in cases of larger heart mass, Tromp et al. [61] indexed EAT mass to heart mass, revealing that the indexed EAT mass was lower in the HFrEF group when compared to the control. Thus, for CMR studies, it is necessary to measure EAT mass and adjust for body surface area.

Although the exact explanation for different status of EAT according to HF classification is not clear, we can propose some possible explanations. Studies with HFrEF mainly enrolled patients with ischemic cardiomyopathy and dilated cardiomyopathy. These advanced HF conditions not only leads to LV dysfunction but also RV dysfunction, followed by intestinal congestion. Intestinal congestion in HF can lead to anorexia and poor nutrition absorption, resulting in catabolic conditions such as sarcopenia [62]. This might be related to the decreased volume of EAT in HFrEF. Conversely, HFpEF is frequently accompanied by obesity, and this induces an increase in intravascular volume, which imposes hemodynamic stress by increasing myocardial workload [30]. Given the higher proportion of obese patients in HFpEF, EAT volume may increase in HFpEF. However, this issue requires further precise research focused on the classification of HFrEF and HFpEF. Pugliese et al. [63] conducted a more advanced study analyzing EAT thickness in patients with HFrEF, HFpEF, and controls and investigated the association between EAT thickness and multiple biomarkers and cardiorespiratory fitness evaluated by peak oxygen consumption. Increased EAT thickness was associated with worse cardiorespiratory fitness, biomarker profile, RV-pulmonary arterial uncoupling, and mortality in patients with HFpEF. Conversely, reduced EAT thickness was associated with worse LV dysfunction and mortality in patients with HFrEF. This study showed that EAT had a pathophysiological role in the characterization of HFrEF and HFpEF. Because EAT has a brown adipose tissue-like function, it serves as an energy reservoir and reflects the catabolic status of HFrEF. In HFpEF, EAT is associated with a worse biomarker profile, suggesting enhanced EAT activity. In HFpEF, EAT maybe associated with hemodynamic stress and poor cardiorespiratory fitness, leading to increased adverse events. In the study with HF with midly reduced ejection fraction and HFpEF, EAT accumulation was associated with the adverse prognosis after adjusting for the conventional risk factors and the severity of HF [64].

Contrary to the findings of various studies on EAT and prevalent HF, the implications of EAT burden on the development of HF have rarely been investigated. The Multi-Ethnic Study of Atherosclerosis group explored whether the baseline pericardial fat volume, including epicardial and pericardial fat, was linked to the occurrence of HF [65]. In this study, pericardial fat volume was evaluated in 6,785 community-based individuals by CT. Pericardial fat volume was linearly associated with an increased risk of HF after adjustment for baseline characteristics, including anthropometric parameters (1-standard deviation increase in pericardial fat volume: hazard ratio, 1.22; 95% confidence interval, 1.12 to 1.31; $P<0.001$). In the Jackson Heart study with 2,882 participants without prevalent HF, a higher volume of PAT and VAT was associated with an increased risk of HFpEF. Although the replication of these findings is warranted in other community-based studies, this study suggested that increasing the amount of EAT in a community-based population might be a novel risk factor for newly diagnosed HF.

EAT AS A POTENTIAL FOR THERAPEUTIC TARGET

EAT can be visualized and quantified using two-dimensional echocardiography or other imaging modalities. EAT volume changes more quickly than other anthropometric parameters of body fat [66]. The role of EAT as a therapeutic target has been elucidated using several emerging cardiovascular drugs. A randomized controlled trial (RCT) evaluated the effect of an intensive dose of atorvastatin and a moderate dose of pravastatin on the progression of the coronary calcium score evaluated by CT [67]. The investigators also evaluated the effect of statins on changes in the EAT volume. Only the intensive-intensity statin group showed significantly decreased EAT volume but not the moderate-intensity group. The degree of lipid reduction did not correlate with EAT regression. This finding suggested that the effect of statins on EAT volume might be related to pleiotropic effects, such as anti-inflammatory effects, and not lipid-lowering effects. In patients with aortic stenosis, statin treatment was associated with lower EAT thickness and an *in vitro* statin-modulated inflammatory profile of human EAT [68]. In patients with coronary artery stenosis, the use of 20-mg atorvastatin was associated with lower EAT thickness than that with the use of 10-mg simvastatin and ezetimibe [69]. However, the effects of statins on EAT thickness in patients with HF require further investigation.

The lipolytic effect of sodium glucose cotransporter 2 (SGLT2) inhibitors, known as the statins of the 21st century [70], has been investigated with a focus on VAT, including EAT [71]. SGLT2 inhibitors increase glucose excretion in the urine, leading to reduced blood glucose levels. Consequently, insulin secretion decreases, and the release of glucagon, which has counter-regulatory effects, increases. Unlike insulin, which promotes lipogenesis and lowers blood glucose, glucagon stimulates lipolysis, elevating blood glucose levels. In other words, SGLT2 inhibitors promote the lipolysis through increased glucagon secretion, as evidenced by several studies showing that the use of SGLT2 inhibitors can reduce visceral obesity [72,73]. Lipolysis results in an increase in blood ketone levels, which can explain one of the notable side effects of SGLT2 inhibitors, known as ketoacidosis.

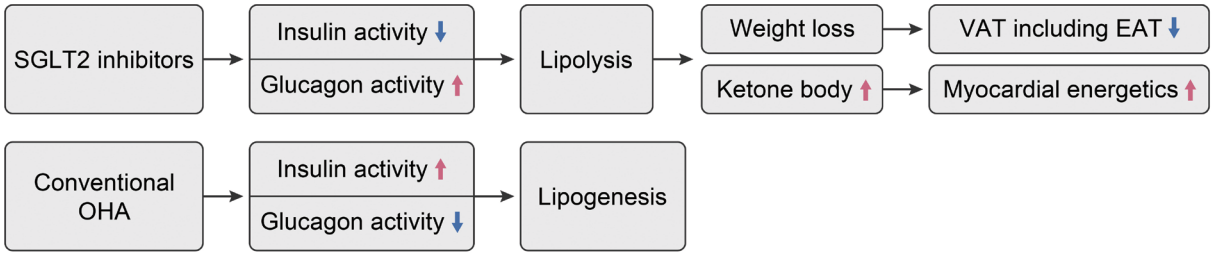

Fig. 5. Mechanism of sodium glucose cotransporter 2 (SGLT2) inhibitor reducing epicardial adipose tissue (EAT). VAT, visceral adipose tissue; OHA, oral hypoglycemic agent.

Table 2. Major clinical studies investigating the role of SGLT2 inhibitors on EAT volume

Study	Population	Imaging modality	Study type	Drug	Control	Duration, wk	Major findings
Requena-Ibanez et al. (2021) [81]	HFrEF (n=84)	CMR	RCT	Empagliflozin	Placebo	24	Empagliflozin significantly reduced EAT volume, myocardial fibrosis, and inflammatory markers compared with placebo
Gaborit et al. (2021) [77]	T2DM (n=56)	CMR	RCT	Empagliflozin	Placebo	12	No effect on myocardial or epicardial fat volume
Hiruma et al. (2021) [78]	T2DM without CVD (n=44)	CMR	RCT	Empagliflozin	Sitagliptin	12	No effect on myocardial or epicardial fat volume
Iacobellis et al. (2020) [79]	T2DM & obesity (n=100)	Echocardiography	RCT	Dapagliflozin	Placebo	24	Dapagliflozin reduced EAT thickness by 20% from baseline

SGLT2, sodium glucose cotransporter 2; EAT, epicardial adipose tissue; HFrEF, heart failure with reduced ejection fraction; CMR, cardiac magnetic resonance; RCT, randomized controlled trial; T2DM, type 2 diabetes mellitus; CVD, cardiovascular disease.

Interestingly, blood ketones serve as an efficient metabolic energy source for the heart. Given the heart's continuous need for hemodynamic energy, it relies on various substances as energy sources, making it a 'metabolic omnivore.' Since ketone produce highest adenosine triphosphate via ketone oxidation, ketone is often referred to as 'the superfuel of the heart.' This rise in blood ketone levels enhances the energy efficiency of the heart, leading to an improved prognosis for HF. In a non-diabetic pig model, use of SGLT2 inhibitor improved myocardial energetics and increased the myocardial ketone uptake [74]. This may explain the outstanding findings of improved HF-related outcomes with SGLT2 inhibitors (Fig. 5) [75]. Based on these findings, the effect of SGLT2 inhibitors on lowering EAT volume and activity has been studied in several studies, including RCTs [72,76-81]. Table 2 summarizes the major RCTs that have investigated the effects of SGLT2 inhibitors on EAT volume. The Iacobellis group studied the effect of dapagliflozin compared to placebo in patients with type 2 diabetes mellitus with a BMI ≥27 kg/m^2 [79]. Dapagliflozin reduced EAT thickness by 20% from baseline in 6 months. The reduction in EAT thickness was higher in the dapagliflozin group than in the metformin group. In this study, the reduction in EAT thickness did not correlate with weight loss, suggesting that the EAT reduction effect of SGLT2 inhibitors might be mediated beyond weight loss. Requena-Ibanez et al. [81] performed an RCT comparing empagliflozin and placebo in patients with HFrEF without diabetes. Empagliflozin reduced the EAT volume compared to the placebo, as evaluated by cardiac MRI after 6 months. EAT reduction was associated with improvements in inflammatory biomarkers, myocardial fibrosis, and aortic stiffness. The lipolytic effect of SGLT2 inhibitors on EAT volume varies according to the study population, drugs, study duration, and imaging modalities. A few studies have failed to demonstrate the effects of SGLT2 inhibitors on EAT volume [77,78]. These studies enrolled a small-sized population with a low cardiovascular risk, and the study period was short. A meta-analysis of RCTs concluded that SGLT2 inhibitors significantly reduced EAT volume in patients with type 2 diabetes mellitus [80]. The effect of SGLT2 inhibitors on the amount of EAT and whether the intervention-induced reduction of EAT volume or activity leads to the improvement in clinical outcomes of HF remains unclear. Therefore, further studies are required to address this issue.

A recent study demonstrated that glucagon-like peptide-1 receptor agonists (GLP-1RA) improved quality of life in patients with HFpEF and obesity [82]. GLP-1RA also exhibit pleiotropic effects, such as weight loss and cardiovascular protection beyond glucose control. They reduce appetite, delay gastric emptying, and can even alter body fat distribution [72]. EAT expresses receptors for GLP-1, and GLP-1RA have been found to be associated with increased gene expression related to the differentiation of white to brown adipose tissue and decreased expression of pro-adipogenic genes [83]. In light of this background, researchers have explored the effects of GLP-1RA injection on EAT. In patients with type 2 diabetes mellitus and obesity, a 24-week liraglutide treatment successfully reduced echocardiographic EAT thickness from 9.6±2.0 to 6.2±1.5 mm, marking a 36% reduction [84]. Long-acting GLP-1RA, such as semaglutide, also decreased EAT thickness in a dose-dependent manner [85]. In a study involving liraglutide, the reduction in EAT thickness was independently correlated with LV mass reduction [84]. This suggests that the reduction of EAT thickness by GLP-1RA could serve as a surrogate marker for myocardial reverse remodeling. Further studies are needed to investigate the association between EAT reduction and cardiovascular protection.

CONCLUSIONS

EAT is a promising biomarker for identifying the HF phenotype and guiding treatment strategies because of its close anatomical and functional connection with the myocardium. It is easily measurable and modifiable, which makes it an attractive therapeutic target. As contemporary medicine for HF emphasizes individualized approaches based on HF phenotypes, further studies are required to fully explore the therapeutic potential of EAT.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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