Perspective

Drugs That Ameliorate Epicardial Adipose Tissue Inflammation May Have Discordant Effects in Heart Failure With a Preserved Ejection Fraction as Compared With a Reduced Ejection Fraction

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ABSTRACT

Heart failure with a preserved ejection fraction (HFpEF) and heart failure with a reduced ejection fraction (HFrEF) have distinctive pathophysiologies, and thus, therapeutic approaches to the 2 disorders should differ. Neurohormonal activation drives the progression of HFrEF, and neurohormonal antagonists are highly effective in HFrEF, but not in HFpEF. Conversely, a broad range of chronic systemic inflammatory or metabolic disorders cause an expansion and inflammation of epicardial adipose tissue; the secretion of adipocytokines may lead to microvascular dysfunction and fibrosis of the underlying myocardium, which (if the left atrium is affected) may lead to atrial fibrillation (AF) and (if the left ventricle is affected) may lead to HFpEF. Anti-inflammatory drugs (such as statins and anticytokine agents) can ameliorate epicardial adipose tissue dysfunction. Statins appear to ameliorate the development of atrial myopathy (both experimentally and clinically), and in randomized controlled trials, they reduce the incidence of new-onset and recurrent AF and decrease the risk of heart failure with the features of HFpEF; yet, they have no benefits in HFrEF. Similarly, anticytokine agents appear to prevent heart failure in patients with or prone to HFpEF, but adversely affect HFrEF. Several antihyperglycemic agents also reduce epicardial fat mass and inflammation, but this benefit may be offset by additional actions to cause sodium retention and neurohormonal activation. Thiazolidinediones have favorable effects on experimental AF and HFpEF, but their antinatriuretic actions negate these benefits, and they worsen the clinical course of HFrEF. Glucagon-like peptide-1 receptor agonists also ameliorate AF and HFpEF in laboratory models, but their positive inotropic and chronotropic effects may be deleterious in HFrEF. By contrast, metformin and sodium-glucose cotransporter 2 inhibitors alleviate epicardial adipose tissue dysfunction and may reduce the risk of AF and HFpEF; yet, they may have additional actions to promote cardiomyocyte survival that are useful in HFrEF. The concordance of the benefits of anti-inflammatory and antihyperglycemic drugs on AF and HFpEF (but not on HFrEF) supports the paradigm that epicardial adipose tissue is a central pathogenetic mechanism and therapeutic target for both AF and HFpEF in patients with chronic systemic inflammatory or metabolic diseases. (*J Cardiac Fail 2019;25:986–1003*)

Key Words: Epicardial adipose tissue, heart failure with preserved ejection fraction, atrial fibrillation, atrial myopathy.

The 2 main phenotypes of chronic heart failure are heart failure with a reduced ejection fraction (HFrEF) and heart failure with a preserved ejection fraction (HFpEF). HFrEF is characterized primarily by the loss and stretch of cardiomyocytes, which often follows a clinically overt myocardial injury (eg, myocardial infarction). Systolic ejection is impaired, and cardiac chambers are markedly enlarged and remodeled.[1] In contrast, HFpEF is typically linked to a systemic inflammatory or metabolic disorder, which can directly impair the endothelial function of the coronary microvasculature.[2,3] In addition, these

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disorders may alter the biology of epicardial adipose tissue, which may further amplify the effects of the systemic disorder onto the underlying myocardium; the resulting microvascular derangement and fibrosis of the atrial and ventricular myocardium may lead to atrial fibrillation (AF) and HFpEF, respectively.[4–6] In these patients, systolic function is relatively preserved, but atrial electrical activation is disturbed and ventricular distensibility is impaired; as a result, the volumes of the cardiac chambers are only modestly increased.[7,8] Biomarkers of systemic inflammation are prominent, and these are accompanied by evidence of end-organ dysfunction and multiple clinical comorbidities.[1,9,10]

Contrasting Therapeutic Approaches to HFrEF and HFpEF

Because of these contrasting mechanisms, therapeutic approaches to HFrEF and HFpEF differ. Drugs that prevent the neurohormonally-driven remodeling of the left ventricle are highly effective in HFrEF, but not in HFpEF. Specifically, inhibitors of the renin-angiotensin system reduce the risk of death or hospitalization for heart failure in HFrEF, but have only modest or negligible effects in HFpEF.[11,12] Similarly, beta-blockers, mineralocorticoid receptor antagonists and neprilysin inhibitors reduce mortality markedly in patients with HFrEF,[13–15] but the magnitude of their benefits in patients with HFpEF are much less striking and may be primarily driven by favorable effects in patients with an ejection fraction of 40%–50%.[16–19] Sinus node slowing with ivabradine reduces the risk of heart failure hospitalizations in HFrEF,[20] but the drug worsened the functional capacity of patients with HFpEF in 2 randomized controlled trials.[21,22]

Is the converse proposition also true? Do agents that preferentially benefit HFpEF have minimal or (perhaps) deleterious effects in HFrEF? Although there are no established therapies for HFpEF, new treatments for HFpEF are being actively explored; specifically, there is interest in drugs that can reduce the mass and inflammatory state of epicardial adipose tissue.[4] If dysfunctional epicardial fat leads to inflammation of both the atrial and ventricular myocardium, then interventions that ameliorate this abnormality might exert favorable effects on both AF and on HFpEF.[4] By contrast, epicardial adipose tissue is not increased and appears to play a nutritive role in HFrEF,[23,24] and thus, the anti-inflammatory action of antiadipogenic interventions might not be useful in this disorder. Furthermore, drugs that target epicardial adipose tissue may exert additional deleterious effects (ie, to promote renal sodium excretion or neurohormonal activation) that can lead to adverse clinical outcomes in patients with HFrEF.

Role of Systemic and Epicardial Adipose Tissue Inflammation in the Pathogenesis of AF and HFpEF

Many disorders that are characterized by systemic or adipose tissue inflammation have been closely linked to both AF and HFpEF. The incidence of AF is increased in association with the chronic inflammation seen in rheumatoid arthritis, ankylosing spondylitis, psoriasis, systemic sclerosis, chronic HIV and viral hepatitis infection, and inflammatory bowel disease as, well as the metabolic derangements seen in obesity, diabetes, and primary hyperaldosteronism.[25–34] The prevalence of AF has been established based on observations made during routine electrocardiography; the associations could be meaningfully stronger if implanted devices were used to detect atrial arrhythmias.[35] At the same time, rheumatoid arthritis, ankylosing spondylitis, systemic sclerosis, psoriasis, chronic HIV and viral hepatitis infection, and inflammatory bowel disease as well as obesity, diabetes, and primary hyperaldosteronism are associated with the development of cardiac fibrosis and microvascular derangements, echocardiographic diastolic filling abnormalities, and heart failure, particularly HFpEF; these findings appear to be directly related to the clinical severity of the systemic inflammatory process or metabolic derangement.[7,36–48]

The striking concordance of both AF and HFpEF in systemic inflammatory and metabolic disorders may be related to an expansion of epicardial adipose tissue,[4] which may act as a transducer to focus the biological derangements of the systemic disorder onto the heart. The epicardium and myocardium are closely intertwined through an unobstructed shared microcirculation; therefore, when systemic inflammatory and metabolic disorders cause epicardial adipocytes to proliferate, the expansion transforms the normal nutritive functions of epicardial fat to a proinflammatory state. The secretion of adipocytokines from dysfunctional epicardial adipose tissue leads to inflammation, microvascular dysfunction, and fibrosis of the underlying myocardium.[4–6,49] If the afflicted epicardial fat surrounds the left atrium, the result may be electroanatomical fragmentation and structural remodeling, leading to AF. When the dysfunctional fat adjoins the left ventricle, the result may be an impairment of ventricular distensibility such that the chamber cannot accommodate an increase in volume without a disproportionate increase in pressure, thus leading to HFpEF.[4,7]

The importance of the epicardium is highlighted by the fact that that each of the systemic inflammatory and adipogenic metabolic disorders that are linked to both AF and HFpEF are also accompanied by an expansion of epicardial adipose tissue mass.[50–58] Furthermore, increases in epicardial fat volume and deleterious changes in its biology are characteristically seen in (and typically precede the onset of) AF and HFpEF in the general population as well as in patients at risk, regardless of the clinical etiology, and are strongly associated with underlying electroanatomical abnormalities and cardiac fibrosis.[59–65] Importantly, both experimentally and clinically, excision of epicardial fat improves the structure and function of the underlying cardiac and vascular tissues (Fig. 1).[66,67]

Effects of Interventions That Attenuate Epicardial Adipogenesis and Adipocyte Inflammation on the Clinical Course of AF and HFpEF

Obesity is not only an adipogenic state, but it is also a systemic inflammatory disorder. For both reasons, obesity increases epicardial adipose tissue mass and leads to atrial electrical derangements as well as diastolic filling

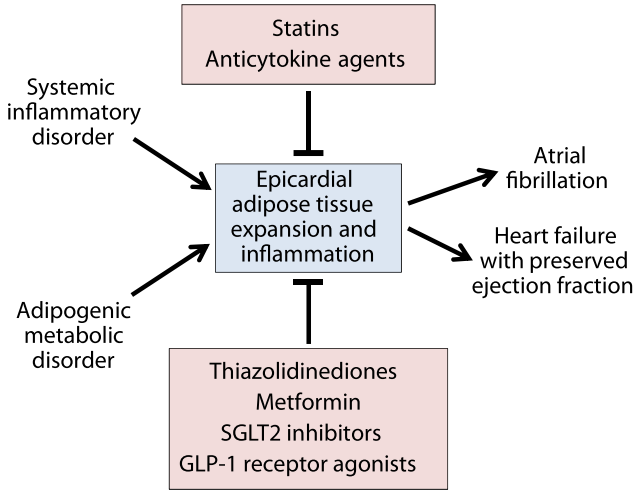

Fig. 1. Proposed role for epicardial adipose tissue expansion and inflammation in the pathogenesis and potential treatment of AF and HFpEF in patients with a chronic systemic inflammatory and adipogenic metabolic disorder.

abnormalities.[56,62,68] As a result, obese people are at markedly increased risk of both AF and heart failure,[32,69,70] and meaningful weight loss reduces epicardial adiposity and ameliorates the development of both AF and heart failure.[71–77] Importantly, the pathophysiological derangements in obesity predispose to the development of HFpEF,[7,78] and the benefits of weight loss on the clinical course of heart failure has been primarily seen in patients with HFpEF, who experience improved diastolic filling dynamics, symptoms, and exercise tolerance.[79–81] In contrast, in patients with systolic dysfunction, weight loss produces only marginal changes in ejection fraction, and the benefit is particularly attenuated in patients with a prior myocardial infarction (who are prone to HFrEF).[82]

Does the proposed framework apply to pharmacologic interventions? If so, then drugs that inhibit epicardial adipose tissue expansion and inflammation should have favorable effects on AF and on HFpEF in patients with systemic diseases and comorbidities. Conversely, these antiadipogenic and anti-inflammatory drugs might not be expected to exert benefits in HFrEF.

Effects of Anti-Inflammatory Drugs on Epicardial Adipose Tissue, AF, and HFpEF

Two classes of anti-inflammatory agents have been evaluated for their effects on adipose tissue inflammation and on its cardiovascular consequences (Table 1): 1) statins, which are used to reduce the risk of atherosclerotic ischemic events in patients with metabolic disorders (eg, dyslipidemia and type 2 diabetes); and 2) anticytokine drugs, which are used for the treatment of systemic inflammatory disorders (eg, rheumatoid arthritis, psoriasis, and inflammatory bowel disease).

Statins. Although their anti-inflammatory effects were first identified in patients with atherosclerotic coronary artery disease, statins have been used to ameliorate biomarkers of inflammation and clinical measures of disease activity in patients with a broad range of systemic inflammatory disorders (eg, rheumatoid arthritis, ankylosing spondylitis, psoriasis, systemic sclerosis, viral hepatitis, and inflammatory bowel disease) as well as in adipogenic metabolic disorders.[83–89] These anti-inflammatory actions of statins may also be responsible for their ability to ameliorate the expansion and inflammation of epicardial adipose tissue in patients with dyslipidemias, inflammatory and metabolic disorders and established cardiovascular disease, including AF.[90–93]

The anti-inflammatory action on the epicardium may explain why statins ameliorate the development of structural and functional abnormalities characteristic of an atrial myopathy in experimentally-induced cardiac stress and in patients with AF,[94–96] and in randomized controlled trials, statins have consistently reduced the incidence of new-onset as well as recurrent AF.[97–99] Additionally, statins ameliorate inflammatory processes in epicardial fat and produce favorable effects on cardiac remodeling in experimental models[91,100] and improve diastolic filling dynamics in the clinical setting.[101–103] Accordingly, the use of statins in patients with systemic inflammatory disorders has been accompanied by a decrease in heart failure biomarkers and a reduced risk of heart failure events.[104–107] Most importantly, in randomized controlled clinical trials in patients with dyslipidemias, statins reduced the risk of new-onset heart failure without preventing the occurrence of an interim myocardial infarction, indicating a benefit on the development of HFpEF.[108] Statins may also reduce the risk of death in patients with an established diagnosis of HFpEF, including the occurrence of noncardiovascular death.[109–111] In marked contrast to these benefits on both AF and HFpEF, treatment with statins produced no benefits on morbidity and mortality in patients with HFrEF in 2 large-scale randomized placebo-controlled clinical trials.[112,113]

Anticytokine Agents. Numerous studies have shown that tumor necrosis factor-α and interleukin 1-β are synthesized and released from inflamed epicardial adipose tissue,[114–117] and circulating levels of both cytokines and other inflammatory biomarkers are elevated in patients with AF and HFpEF, but not in those with HFrEF.[1,118] In the experimental setting, both proinflammatory cytokines and other members of the interleukin-1 family have been directly implicated in the pathogenesis of AF[119–121] and of the ventricular fibrosis and diastolic filling abnormalities seen in HFpEF.[122,123] In these animal models, modulation of tumor necrosis factor and interleukin activity ameliorates the structural abnormalities leading to both AF and HFpEF.[120,124] However, anticytokine agents may promote the synthesis of aldosterone, thereby causing sodium retention, which may exacerbate heart failure.[125]

These observations are relevant to the use of anticytokine agents in the clinical setting. In an observational analysis, the use of antagonists of tumor necrosis factor-α in patients with rheumatoid arthritis (who are prone to HFpEF) was associated with a reduced risk of heart failure events.[126] In a small randomized controlled trial, the interleukin-1

Table 1. Effect of Anti-Inflammatory and Anti-Adipogenic Drugs on Epicardial Adipose Tissue Mass and the Risk of Atrial Fibrillation and Heart Failure With a Preserved or Reduced Ejection Fraction

Drug Class	Effect on Epicardial Adipose Tissue	Other Actions Relevant to Heart Failure	Effect on Atrial Fibrillation	Effect on HFpEF in Clinical Setting	Effect on HFrEF in Clinical Setting
Statins	Reduced mass and inflammation of adipose tissue[89–93]	—	Decreased new-onset and recurrent AF[97–99]	Reduced risk of heart failure without interim myocardial infarction[108]; reduced mortality in established HFpEF[109–112]	No benefit in established HFrEF[112,113]
Anticytokine agents (antagonists of tumor necrosis factor-α and interleukin-1)	Cytokines secreted from epicardial fat,[114–117] but effect of anticytokine agents not evaluated	? Stimulation of aldosterone synthesis[125]	Not evaluated	Benefits with anakinra in HFpEF and with canakinumab in patients with systemic inflammation[127,129]	Adverse effects with etanercept and infliximab in HFrEF[130,131]
Thiazolidinediones	Reduced epicardial fat inflammation, despite increase in adipogenesis[139–141]	Sodium retention due to direct effect on renal tubular sodium reabsorption[161]	Reduced AF in observational studies[157,158] but not randomized clinical trials[166]	No increase in risk of heart failure in patients at risk for HFpEF[172]	Worsening heart failure in HFrEF[172–174]
Metformin	Reduced epicardial fat inflammation[186]	?? Cardioprotection by promoting autophagy[176,177]	Reduced AF in observational studies[202]	Reduced risk of heart failure and death from heart failure in type 2 diabetes in observational studies[203–210]	
Sodium-glucose cotransporter 2 inhibitors	Reduced epicardial fat mass and inflammation[228–232]	Natriuresis; protection against metabolic stress and cell death[237–240]	Reduced risk based on sparse events in randomized controlled trials[233]	Reduced risk of heart failure hospitalizations in type 2 diabetes; benefits to prevent both HFpEF and HFrEF[234,239,240]	
Glucagon-like peptide-1 receptor agonists	Reduces epicardial fat mass[262,263]	Positive inotropic and chronotropic effects, potentially mediated by cyclic AMP[274–276]	Increased AF with albiglutide[277]	Little known about effect on HFpEF	Worsening clinical status and increased heart failure events in HFrEF[282,283]
Dipeptidyl peptidase-4 inhibitors	Little known about actions on epicardial fat	Increased chemokine signaling leading to sympathetic activation and cardiac fibrosis[287–290]	Reduced risk in some observational studies but not in randomized controlled trials[294,295]	Increased risk of heart failure hospitalizations in type 2 diabetes, especially if used with insulin[290,303]	

antagonist anakinra reduced systemic inflammation and improved exercise capacity in HFpEF,[127] although these benefits were not confirmed in a second small study.[128] More persuasively, in a large randomized controlled trial of patients with evidence for systemic inflammation (and thus prone to HFpEF), the interleukin 1-β antagonist canakinumab decreased proinflammatory biomarkers and the risk of hospitalizations for heart failure.[129] In marked contrast to these results in HFpEF, antagonists of tumor necrosis factor-α have not produced benefits in HFrEF, and in fact, their use in HFrEF has been associated with worsening clinical status and an increased risk of adverse outcomes in 3 randomized controlled trials.[130,131]

Effects of Antihyperglycemic Drugs on Epicardial Adipose Tissue, AF, and HFpEF

Three classes of anti-hyperglycemic agents have been evaluated for their potential effects on epicardial adipose tissue, AF, and heart failure: 1) thiazolidinediones; 2) metformin and sodium-glucose cotransporter 2 (SGLT2) inhibitors; and 3) incretin-based agents (Table 1).

Thiazolidinediones. Peroxisome proliferator-activated receptor-γ (PPAR-γ) is a member of a nuclear receptor superfamily that acts as a master transcriptional factor to promote differentiation of preadipocytes, and PPAR-γ signaling is a key mechanism by which the epicardium attains its normal nutritive state and secretes adiponectin.[132,133] PPAR-γ agonism calms inflammation, oxidative stress, and hypertrophy in a broad range of tissues, including adipocytes and cardiomyocytes;[134–136] disorders that lead to adipose tissue inflammation impair PPAR-γ expression,[137] and PPAR-γ stimulation reverses the dysfunctional state of epicardial fat.[138] Thiazolidinediones (pioglitazone and rosiglitazone) act as PPAR-γ agonists, and thereby, reduce the inflammation of human epicardial fat[139,140] despite an increase in epicardial adipogenesis;[141] they also appear to ameliorate cardiac inflammation,[142,143] and biomarkers of systemic inflammation,[144,145] independent of their effects on blood glucose. These anti-inflammatory actions have been used therapeutically to treat rheumatoid arthritis, psoriasis, viral hepatitis, and inflammatory bowel disease.[146–149] Accordingly, pioglitazone reduces atrial inflammation and fibrosis and alleviates the predilection for AF in experimental models of cardiac stress.[150–154] Pioglitazone and rosiglitazone also have been shown to alleviate ventricular fibrosis and diastolic filling abnormalities and minimize the development of experimental HFpEF, even if weight increases as a result of adipogenesis.[155,156] In observational studies, the use of pioglitazone has been associated with a lower risk of new-onset or recurrent AF[157,158] and an improvement in abnormal diastolic filling dynamics in patients with type 2 diabetes.[159,160]

However, PPAR-γ agonism is a powerful stimulus to sodium reabsorption in the renal tubules, and therefore, thiazolidinediones cause sodium retention,[161] thereby increasing plasma and cardiac volumes and circulating levels of natriuretic peptides, especially in patients with pre-existing evidence of increased cardiac wall stress.[162–165] The resulting increase in left atrial size seen with these drugs may cause sufficient stretch of the atrial myocardium[163] so as to neutralize the benefits on AF that might be expected to follow their anti-inflammatory effects on epicardial adipose tissue. This may explain why, in large-scale randomized controlled clinical trials, thiazolidinediones have not reduced the frequency of AF events in patients with insulin resistance or type 2 diabetes.[166]

A similar interplay may also occur in the left ventricle. Marked sodium retention would be expected to increase the risk of heart failure, whether it is related to HFpEF or HFrEF. Accordingly, the use of thiazolidinediones has consistently increased the risk of serious heart failure events in randomized controlled trials, especially when the PPAR-γ agonists were added to insulin, which exerts its own antinatriuretic action.[167–171] However, in patients with HFpEF, the anti-inflammatory effect of PPAR-γ agonism on epicardial fat might be expected to ameliorate diastolic filling abnormalities.[159] Such an action might offset the adverse effects of sodium retention, leading to a neutral effect of these drugs on the evolution of HFpEF. In contrast, the anti-inflammatory action of thiazolidinediones might have little relevance in HFrEF; such patients would be exposed to sodium retention without the possibility of an offsetting benefit. Such a framework may explain why, in large-scale clinical trials, pioglitazone worsened the clinical course of patients with HFrEF, including those with a history of prior myocardial infarction;[172,173] in another double-blind randomized controlled trial carried out in patients with systolic dysfunction, pioglitazone increased the risk of heart failure hospitalizations in those with established HFrEF.[174] In contrast, in large-scale cardiovascular outcomes trials, the thiazolidinedione did not increase heart failure events in patients at risk of developing HFpEF.[172]

Metformin and SGLT2 Inhibitors. Independent of its antihyperglycemic action, metformin exerts direct anti-inflammatory effects by its ability to stimulate AMP-activated protein kinase and thereby inhibit nuclear factor κB.[175,176] Accordingly, the use of the drug has been proposed as a treatment of broad range of systemic inflammatory diseases, including rheumatoid arthritis, psoriasis, chronic viral hepatitis, and inflammatory bowel disease, based on both experimental and clinical observations.[176–181] Importantly, metformin promotes the action of adiponectin and suppresses inflammation in adipose tissue,[182–185] and it reduces the secretion of inflammatory cytokines from epicardial fat.[186] Experimentally, the drug protects against microvascular derangements and cardiac fibrosis and hypertrophy,[187–192] thereby ameliorating atrial electrical abnormalities and ventricular remodeling,[193–195] and preventing heart failure, including HFpEF.[196–198] In observational studies carried out in the clinical setting, its use has been associated with the prevention of microcirculatory injury,[199] an improvement in diastolic function,[200,201] a reduced risk of both AF and heart failure,[202–205] and a reduced risk of death in patients with established heart failure.[206–211] However, randomized clinical trials

to confirm these benefits and to characterize the heart failure phenotype that might benefit from metformin are lacking.[212]

SGLT2 protein is increased in states of inflammation, and SGLT2 inhibitors block the activity of the Nlrp3 inflammasome in a broad range of tissues, thus minimizing the release of proinflammatory cytokines.[213–217] SGLT2 inhibitors ameliorate adipocyte hypertrophy and inflammation, thus restoring adipose tissue to its healthy condition,[218–220] and in parallel, they reduce cardiac hypertrophy and fibrosis and prevent the development of heart failure in experimental models of HFpEF.[221–227] In the clinical setting, SGLT2 inhibitors reduce epicardial adipose tissue mass and inflammation,[228–231] and this benefit is accompanied by an improvement in diastolic filling abnormalities[232] and a reduced risk of AF (based on sparse number of events).[233] Most importantly, SGLT2 inhibitors have reduced the risk of heart failure hospitalizations in several large-scale randomized trials in type 2 diabetes.[234] Post hoc analyses of these studies suggest that SGLT2 inhibitors may have benefits in HFpEF.[235,236] However, these drugs have additional effects on the sodium-hydrogen exchange mechanism in cardiomyocytes that might be directly beneficial to patients with HFrEF;[237–240] such benefits may prove to be more important in HFrEF than any actions that these drugs might have on epicardial adipose tissue inflammation.

Incretin-Based Antihyperglycemic Agents. Systemic inflammation interferes with the normal functioning of incretins,[241,242] and glucagon-like peptide-1 (GLP-1) signaling exerts anti-inflammatory effects in a broad range of tissues,[243–246] prompting their potential use in rheumatoid arthritis, psoriasis and inflammatory bowel disease.[247–249] GLP-1 receptor agonists interrupt proinflammatory pathways, which may be responsible for their ability to ameliorate derangements in coronary arteries and myocardium in experimental models of atherosclerosis and inflammation-mediated cardiac injury.[250–257] Signaling through the GLP-1 receptor in adipocytes suppresses proliferation, limits inflammation and promotes a nutritive state,[258–261] which may underlie their action to reduce epicardial adipose tissue mass in patients with type 2 diabetes.[262,263] These actions have been accompanied by salutary effects on atrial electrical activation in experimental models of AF and on myocardial inflammation, ventricular fibrosis, and survival in experimental models of HFpEF.[264–269] GLP-1 receptor agonists have been reported to improve diastolic filling abnormalities in diabetic patients in some studies, but not others.[270–273] However, no clinical studies of GLP-1 receptor agonists in patients with established HFpEF have been carried out.

Nonetheless, independent of any effect of these drugs on epicardial adipose tissue mass and inflammation, GLP-1 receptor agonists can stimulate cyclic AMP and increase heart rate and contractility in experimental HFrEF and in human myocardium, and such actions could potentiate the deleterious effects of sympathetic activation in patients with HFrEF or AF.[274–276] In a meta-analysis of randomized controlled trials, new-onset AF occurred more commonly in patients treated with the GLP-1 receptor agonist albiglutide than in the comparator groups.[277] In patients with impaired systolic function, liraglutide increased heart rate and enhanced cardiac contractility, and the magnitude was greater than with increased GLP-1 signaling produced by dipeptidyl peptidase 4 (DPP-4) inhibition.[278–281] In 2 randomized clinical trials in patients with HFrEF, liraglutide led to worsening clinical status, worsening renal function, and an increased risk of serious heart failure, despite a decrease in body weight.[282,283] If GLP-1 receptor agonists exert deleterious effects in HFrEF but favorable effects on HFpEF, these offsetting actions may explain the neutral effect on heart failure events when these drugs have been evaluated in large-scale cardiovascular outcomes trials,[284–286] because patients with type 2 diabetes are at risk of both HFrEF and HFpEF. Phenotypic characterization of the heart failure events in these trials will be highly informative in supporting or refuting this hypothesis.

Increased GLP-1 signaling can also be achieved by DPP-4 inhibition, but the actions of DPP-4 inhibitors differ from those of GLP-1 receptor agonists, in that DPP-4 inhibitors potentiate the effects of stromal cell-derived factor, a chemokine that stimulates the sympathetic nervous system and promotes cardiac fibrosis,[287,288] explaining why DPP-4 inhibition can worsen cardiac fibrosis experimentally.[289] Both effects would be expected to exacerbate AF and heart failure.[290] Although some experimental studies and observational analyses have suggested a benefit on DPP-4 inhibitors on AF,[291–293] this effect has not been confirmed in other studies or in randomized controlled trials.[294,295] Similarly, despite favorable effects on heart failure seen in certain animal models,[296,297] an increased risk of heart failure has been reported in observational studies and randomized controlled trials.[298] In the randomized controlled clinical trials, vildaglipin produced adverse effects on ventricular remodeling,[299] and saxagliptin and alogliptin (but not sitagliptin or linagliptin) increased the risk of heart failure events.[300–303] Because these drugs are insulin secretagogues, it is noteworthy that a recent analysis has suggested that the antinatriuretic action of insulin may potentiate this risk;[290] even with linagliptin, a higher heart failure risk was seen when the drug was administered concurrently with insulin.[303] Most interestingly, the proinflammatory actions of chemokine potentiation would be expected to negate any ability of enhanced GLP-1 signaling to attenuate adipose tissue dysfunction.[304] Interestingly, little is known about the effects of DPP-4 inhibitors on epicardial adipose tissue mass,[305] but the benefits of these drugs on adipocyte biology are modest.[306] This may explain why these drugs may not have preferential benefits on HFpEF, although further study is needed.[303]

Synthesis and Future Directions

Numerous systemic inflammatory and metabolic disorders are accompanied by an increased risk of both AF and HFpEF, potentially because they all act to increase the mass and inflammatory features of epicardial adipose tissue. Certain interventions that are currently used in the management of these diseases can reduce epicardial fat thickness and

ameliorate its inflammatory characteristics; these actions have been accompanied by a decrease in microcirculatory dysfunction (and possibly fibrosis), leading to a reduction in atrial arrhythmogenesis and amelioration of abnormalities of diastolic filling. These effects may contribute meaningfully to the favorable effects on both AF and on HFpEF that have been reported in observational analyses and randomized controlled trials. The concordance of these benefits supports the framework that epicardial adipose tissue is an important pathogenetic mechanism for both AF and HFpEF in patients with chronic systemic inflammatory or metabolic diseases, and that epicardial adiposity is a key target for therapeutic interventions that are directed to the management of both AF and HFpEF.

However, it is not clear that epicardial adipose tissue expansion and inflammation are important in the pathogenesis of HFrEF. Furthermore, many agents that act on epicardial biology have additional effects, particularly to promote sodium retention by the kidneys or to cause the activation of neurohormonal systems. These actions might limit or negate some of the benefits on AF and HFpEF that might otherwise be seen with these treatments, but more importantly, their deleterious actions may cause worsening heart failure in patients with HFrEF who are not poised to benefit from drugs that target the epicardium. The differential effects of drugs in HFrEF and HFpEF highlight the distinctive pathogenetic mechanisms that drive these 2 disorders.

Ongoing studies are poised to provide further support or potentially refute the proposed framework. Large-scale randomized controlled trials of SGLT2 inhibitors in both HFpEF and HFrEF are underway, and mechanistic studies are planned to determine whether these benefits are related to the effects of these drugs on epicardial adipose tissue.[307,308] Analyses of completed cardiovascular outcomes trials with GLP-1 receptor agonists should provide important insights into the possibility for differential effects in patients with HFpEF and HFrEF. Finally, formal randomized controlled trials are warranted and needed to evaluate the potential benefits of statins, metformin, and canakinumab in patients with confirmed HFpEF, who do not already have an established indication for the use of these drugs. If these studies include assessments of epicardial adipose tissue mass and cardiac fibrosis by magnetic resonance imaging, they are likely to provide important mechanistic insights even if they do not enroll a large number of patients. However, large definitive trials will be needed to demonstrate their potential utility in preventing or treating AF or HFpEF in patients with a chronic systemic inflammatory or adipogenic metabolic disorder.

Disclosures

Dr. Packer has recently consulted for Abbvie, Actavis, Akcea, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Cardiorentis, Daiichi Sankyo, Gilead, Johnson & Johnson, NovoNordisk, Pfizer, Relypsa, Sanofi, Synthetic Biologics, and Theravance. None of these relationships are relevant to the topic of this paper.

Supplementary materials

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