Circulation: Heart Failure

ADVANCES IN HEART FAILURE, MECHANICAL CIRCULATORY SUPPORT AND TRANSPLANT

Cellular Interactions and Immunometabolic Mechanisms in Heart Failure With Preserved Ejection Fraction: From Molecular Mechanisms to Clinical Evidence

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ABSTRACT: Heart failure with preserved ejection fraction (HFpEF) is a complex clinical syndrome affecting ≈32 million individuals worldwide. It accounts for at least half of all heart failure cases and is associated with substantial morbidity and mortality. Although the prevalence of HFpEF increases with age, a substantial proportion of the HFpEF subjects present with cardiometabolic alterations, marking a specific phenogroup of HFpEF. Obesity, diabetes, and hypertension are considered central features in the pathophysiology of HFpEF, driving its development and disease progression by a complex interplay of metabolic-, hemodynamic-, and neurohormonal impairments, resulting in systemic inflammation and immune system dysregulation. Cellular and systemic immunometabolic stress induces vascular endothelial microvascular dysfunction, infiltration of immune cells in the myocardium, and activation of innate and adaptive immune cells in cardiac tissue. The resulting bidirectional crosstalk between systemic and cardiac metabolism influences immune cell reprogramming, sustaining a vicious cycle of cardiac chronic inflammatory response, ultimately leading to adverse structural and functional cardiac remodeling. In this review, we discuss the role of cellular interactions and immunometabolic mechanisms of immune system dysregulation resulting in cardiometabolic HFpEF and elaborate on therapeutic strategies targeting cardiometabolic risk.

Key Words: heart failure ■ hypertension ■ immune system ■ inflammation ■ obesity

Heart failure (HF) with preserved ejection fraction (HFpEF) is a multifaceted clinical syndrome impacting roughly 32 million people worldwide. It represents at least half of all HF cases and is linked to significant morbidity and mortality.[1] The prevalence of HFpEF rises with age, and HFpEF is slightly more common in women.[2] A significant subset of patients with HFpEF exhibits cardiometabolic alterations, including obesity, diabetes, and hypertension, driving HFpEF pathophysiology and disease progression by a complex interplay of metabolic-, hemodynamic-, and neurohormonal impairments.[1] These systemic perturbations lead to a chronic low-grade systemic inflammatory state accompanied by subsequent systemic immune response and dysregulation.[3] Myocardial immunometabolic stress leads to coronary microvascular endothelial dysfunction, infiltration of immune cells in the myocardium, and activation of innate and adaptive immune cells in cardiac tissue, resulting in adverse structural and functional cardiac remodeling featuring HFpEF.[3] Here, we discuss the role of cellular interactions and immunometabolic mechanisms of immune system dysregulation in cardiometabolic HFpEF and elaborate on contemporary and future therapeutic options targeting cardiometabolic risk.

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Circulation: Heart Failure is available at www.ahajournals.org/journal/circheartfailure

Nonstandard Abbreviations and Acronyms

AMPK	AMP-activated protein kinase
Angptl4	angiopoietin-like 4
ATM	adipose tissue macrophage
CCL	CC-chemokine-ligand
CCR2	CC chemokine receptor 2
CRP	C-reactive protein
DNase	deoxyribonuclease
EC	endothelial cell
ECM	extracellular matrix
eNOS	endothelial NO synthase
FAP	fibroblast activation protein
FoxO1	forkhead box O1
FOXP	forkhead box P
GIP	glucose-dependent insulinotropic polypeptide
GLP-1	glucagon-like peptide-1
HF	heart failure
HFPEF	heart failure with preserved ejection fraction
HIF1α	hypoxia-inducible factor 1α
HRQL	health-related quality of life
ICAM-1	intercellular adhesion molecule-1
IFN	interferon
IL	interleukin
iNOS	inducible nitric oxide synthase
IRE1α	inositol-requiring enzyme 1 a
LDL	low-density lipoprotein
LDLR	low-density lipoprotein receptor
LIFR	leukemia inhibitory factor receptor
LpL	lipoprotein lipase
MCP-1	monocyte chemoattractant protein-1
MMP-9	matrix metalloproteinase-9
mTOR	mammalian target of rapamycin
MYD88	myeloid differentiation primary response 88
NET	neutrophil extracellular trap
NF-κB	nuclear factor-κB
NLRP	3NOD-, LRR- and pyrin domain-containing protein 3
NT-proBNP	N-terminal pro-B-type natriuretic peptide
PGC1-α	peroxisome proliferator–activated receptor γ coactivator 1-α
SAA	serum amyloid A
SGLT2	sodium-glucose cotransporter 2
SIRT	sirtuin
T reg	T regulatory
T2DM	type 2 diabetes
TGF	transforming growth factor
Th1	T helper
TLR	toll-like receptor
TNF	tumor necrosis factor
VCAM-	1vascular cell adhesion molecule-1
VEGF	vascular endothelial growth factor
VLDL	very low-density lipoprotein
VLDLR	very low-density lipoprotein receptor

INFLAMMATION AND IMMUNE DYSREGULATION IN COMORBIDITIES RELATED TO HFpEF

Inflammation and immune dysregulation are prominent in comorbidities of HFpEF. In obesity, expanded visceral adipose tissue due to adipocyte hyperplasia and hypertrophy acts as an immune-active site, predisposing to meta-inflammation. Hypertrophic adipocytes upregulate chemokines like CCL (CC-chemokine-ligand) 2, CCL5, and CCL8, leading to proinflammatory macrophage recruitment.[4] Moreover, expanded adipocytes undergo hypoxia, promoting oxidative stress, membrane and endoplasmic reticulum stress pathways, and ultimately, adipocyte death.[4] Recruited adipose tissue macrophages (ATMs), which express a proinflammatory M1-like asset and cluster around dead adipocytes forming crown-like structures, secrete TNF (tumor necrosis factor)-α, IL (interleukin)-1β, and IL-6, further promoting proinflammatory signaling and the polarization of other macrophages into an M1-like state.[5] Indeed, individuals with obesity show an up to 40% increased number of ATMs, characterized by a proinflammatory M1-like polarization state,[6] whereas humans and mice without obesity show reduced ATMs ranging from 10% to 15% of all adipose tissue cells, with a predominant anti-inflammatory M2-like asset.[7]

Adipose tissue in obesity is further characterized by an increased number of (CD-cluster of differentiation) 3+CD4+T helper (Th1) cells producing IFN (interferon)-γ,[8] and abundant CD3+CD8+T cells promoting monocyte chemotaxis and monocyte differentiation into ATMs.[9] In addition, the number of $CD3^+CD4^+FOXP3^+$ T regulatory (T reg) cells decreases in obese fat, enhancing proinflammatory activity.[10] Indeed, T reg cells regulate the functions of other T cells, suppress monocyte migration, and promote their shift toward the M1-like anti-inflammatory polarization state.[11] Other immune cells, including neutrophils, natural killer cells, and B-lymphocytes, participate in the chronic inflammatory tone of adipose tissue, modifying functions and polarization of ATMs, which may represent a central mediator of obesity-related downstream effects.[12]

Obesity is strongly associated with type 2 diabetes (T2DM). Fat accumulation in the liver often occurs before

the onset of T2DM and contributes to the reduction of hepatic insulin sensitivity, leading to fasting hyperglycemia, whereas pancreatic fat accumulation further determines beta-cell dysfunction. In adipose tissue, TNF-α and IL-6 released by M1-like ATMs surrounding dead adipocytes promote systemic insulin resistance. TNF-α downregulates the expression of glucose transporters, such as GLUT4, inhibiting glucose uptake by adipocytes and skeletal muscle,[13] and reduces insulin signaling by stimulating inhibitory serine phosphorylation of insulin receptor tyrosine kinase proteins.[14] Conversely, IL-6 inhibits insulin signaling by inducing serine phosphorylation of insulin receptor substrate proteins.[15] Subsequent chronic hyperglycemia triggers inflammatory response through increased oxidative stress, that further compromises insulin signaling.[12] Moreover, adipose tissue inflammation promotes hepatic insulin resistance, impairs skeletal muscle glucose uptake, affects pancreatic insulin secretion, and disrupts endothelial function due to the systemic release of cytokines and free fatty acids. These effects disrupt metabolic homeostasis, sustaining systemic insulin resistance, hyperglycemia, and the progression of T2DM.

Obesity acts as a vicious twin with hypertension. Increases in blood pressure and weight gain synergize by promoting inflammation and immune system dysregulation. Hypertensive patients show elevated levels of inflammatory cells and mediators. Thus, $CD3^+CD8^+$T cells, $CD4^+$ Th17 cells, T reg cells, monocytes, macrophages, and B cells, as well as cytokines and chemokines, such as IL-17, IL-18, IFN-γ, and TNF-α seem to be critical in immune dysregulation associated with hypertension.[16] Chronic activation of the sympathetic nervous system and the renin–angiotensin–aldosterone system, as well as redox signaling imbalance, act as prohypertensive factors, leading to the release of upstream inflammatory mediators. Local inflammation, mechanical and oxidative damage to cells and tissues, lead to the formation of damage-associated molecular patterns and neoantigens.[16] Antigen-presenting cells, including dendritic cells, macrophages, and B cells, present hypertension-specific neoantigens to T cells in lymphoid organs, promoting the activation and infiltration of T and B cells into target organs, such as the heart, vessels, and kidneys.[16] Chronic activation and infiltration of T cells into target organs lead to activated effector and memory cell recruitment, promoting the development of cytotoxic senescent immune cells and organ dysfunction. Downstream effector cytokines as IL-1β, IL-6, TNF-α, IL-17A, and TGF (transforming growth factor) β mediate blood pressure increases, inhibit NO production, and promote oxidative stress, inflammation, fibrosis, and end-organ damage in the heart (ventricular remodeling, hypertrophy), vasculature (endothelial dysfunction, vasoconstriction, vascular remodeling), and kidneys (affected sodium transport).[16]

Obesity, diabetes, and hypertension are frequently accompanied by chronic kidney disease in HFpEF, promoted by vascular injury, metabolic dysregulation, and increased intraglomerular pressure, which all accelerate kidney damage. In addition, the systemic proinflammatory state driven by comorbidities leads to inflammation-mediated renal dysfunction. Inflammatory cytokines, such as IL-6 and TNFα, cause endothelial dysfunction and oxidative stress, impairing renal microcirculation and lowering glomerular filtration rate. Moreover, uremic toxins further fuel inflammation, creating a vicious cycle that worsens both heart and kidney function.[17]

CELLULAR INTERACTIONS IN HFpEF

Systemic Immune Dysregulation and Interactions With the Myocardium in HFpEF

HFpEF develops from systemic comorbidities that may ultimately affect the heart, representing an outside-in mechanism of the disease, which likely triggers adaptive and innate immunity. Indeed, HFpEF is a multisystemic syndrome involving complex interorgan immune and metabolic crosstalk (Figure 1). In this context, the liver has emerged as a key player. A study employing hepatocyte-specific secretome profiling strategy in a murine HFpEF model identified soluble LIFR (leukemia inhibitory factor receptor) as a liver-derived circulating mediator upregulated in HFpEF. LIFR, part of the IL-6 cytokine receptor family, was shown to promote fibroblast activation and profibrotic signaling in the heart via Smad3 phosphorylation, particularly when combined with TGF- 1.[18] Another study employing cross-tissue transcriptomic correlation analysis from HFpEF preclinical models uncovered SAA (serum amyloid A) proteins (SAA1/4) as liver-derived, obesity-independent mediators of inflammation and fibrosis in the heart, potentially driving the metainflammatory component of HFpEF.[19] Thus, beyond resident cardiac immune cells, circulating inflammatory mediators originating from metabolically active organs such as the liver may play a crucial role in HFpEF pathogenesis. The development of myocardial damage from without starts from systemic inflammation and metabolic stress, which systemically trigger vascular endothelium, as well as macrophages, neutrophils, Th1 and Th17 cells infiltration into the myocardium.[3]

Similar to many nonlymphoid organs, the myocardium is composed of various cell types, including cardiomyocytes, fibroblasts, vascular cells, and local immune cells, the majority of which are macrophages. Macrophages reside within the interstitial spaces, where they interact directly with cardiomyocytes, endothelial cells (EC), and fibroblasts. Resident macrophages are a heterogeneous group of phagocytic immune cells that ensure immunosurveillance, tissue homeostasis, and repair. Recent findings in mice and humans suggest their crucial role in

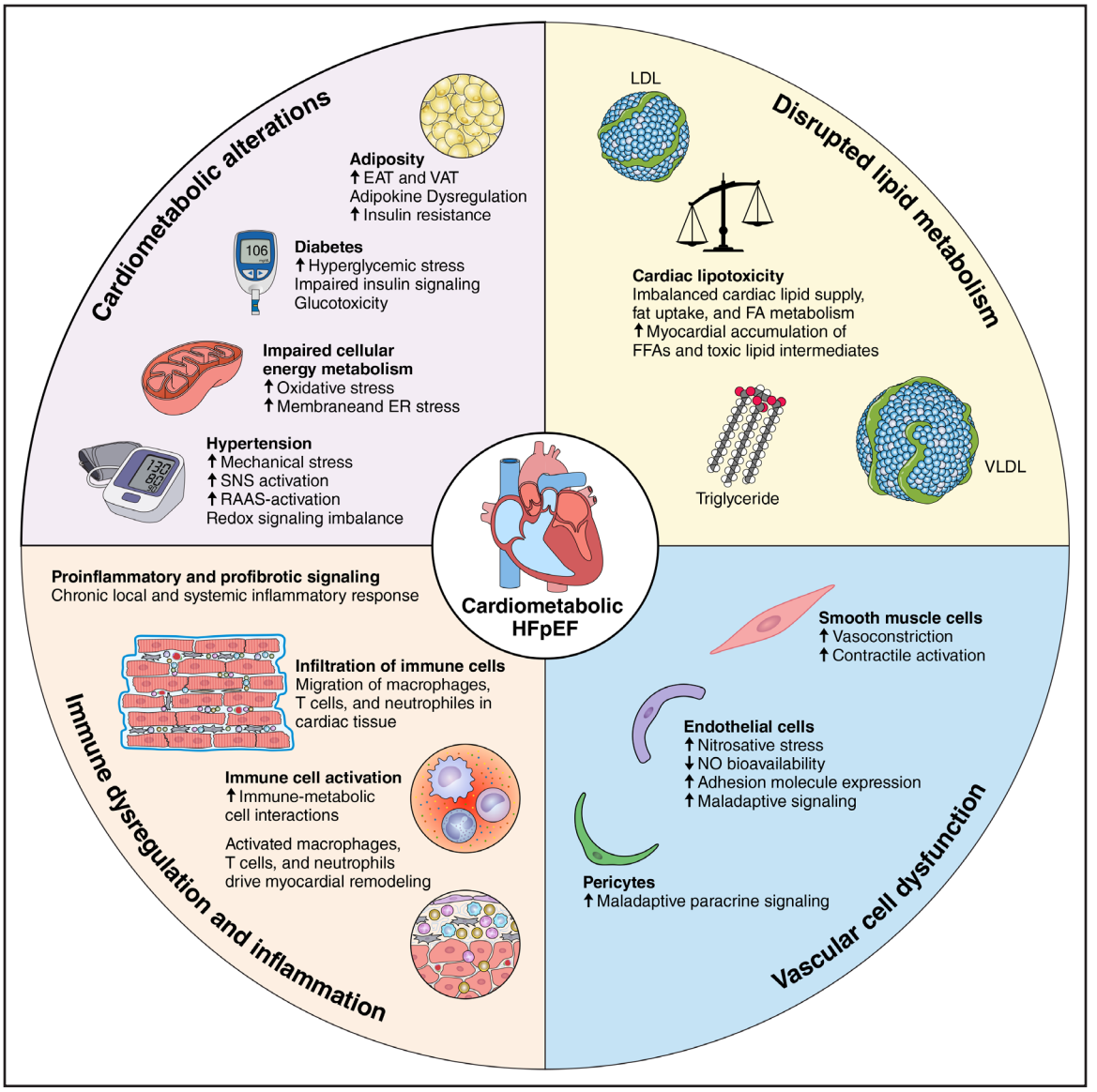

Figure 1. Cellular interactions and immunometabolic mechanisms in cardiometabolic Heart failure with preserved ejection fraction (HFpEF).

EAT indicates epicardial adipose tissue; ER indicates endoplasmic reticulum; FA, fatty acid; FFA, free fatty acid; LDL, low-density lipoprotein; RAAS, Renin-Angiotensin-Aldosterone System; SNS, sympathetic nervous system; VAT, visceral adipose tissue; and VLDL, very low-density lipoprotein.

the protection against pathological stimuli and common comorbidities of HFpEF, including obesity, diabetes, and hypertension.[3] Cardiac tissue–resident macrophages present 2 different origins, detectable based on their negativity or positivity to CCR2 (CC-chemokine receptor 2). The CCR2$^-$ population is embryonic-derived and shows self-renewal activity in the adult heart without significant contribution from circulating monocytes.[20] Conversely, the CCR2$^+$ macrophage population is adult hematopoietic-derived and expresses *Ccr2* at least for a window of time after tissue specification from circulating monocytes. After cardiac injury, CCR2$^+$ macrophages are identified as responsible for the initial recruitment of monocytes through a MYD88 (myeloid differentiation primary response 88)-dependent pathway, modulating the expression of chemoattractant chemokines and monocyte specification. Moreover, these macrophages are critical in tissue inflammation and adverse left ventricular (LV) remodeling. Additionally, aging, a key risk factor for HFpEF, is associated with the replacement of CCR2$^-$ embryonic-derived tissue-resident macrophages with CCR2$^+$ monocyte-derived populations.[21] HFpEF hearts display increased populations of infiltrating CCR2$^+$ macrophages, showing analogies with these findings in aging. Some evidence suggests the potential of inhibiting CCR2$^+$ macrophage activation by suppressing inflammation and adverse remodeling in HF.[22] Conversely, tissue-resident CCR2$^-$ macrophages inhibit

monocyte recruitment, exerting anti-inflammatory and tissue-repairing effects.

Data from endomyocardial biopsies in patients with HFpEF also show a significant increase in cardiac $CD3^+$ T cells compared with healthy controls, indicating the activation of an adaptive T-cell–mediated immune response.[23] Increased circulating levels of Th17 cells are reported, as well as expanded T reg cells expressing CCR6, a known suppressor of regulatory T-cell activity.[24] These findings suggest an imbalance between proinflammatory Th17 cells and anti-inflammatory/suppressive T reg cells. A dysregulated Th17/T reg ratio favoring Th17 cells is regarded as crucial in cardiometabolic disorders. Moreover, endomyocardial biopsy samples from patients with HFpEF revealed increased expression of VCAM-1 (vascular cell adhesion molecule-1), ICAM-1 (intercellular adhesion molecule-1), and E-selectin, all of which are critical for extravasation of T cells and infiltration into the myocardium.[23] In addition, a study on the 2-hit HFpEF mouse model (Nω-nitro-L-arginine methyl ester in conjunction with high-fat diet) revealed an association between diastolic dysfunction, cardiac hypertrophy, and infiltrating T cells with a novel molecular signature. In fact, these cells display impaired IRE1α (inositol-requiring enzyme 1 a)-Xbp1s signaling promoting T-cell cardiotropism independent of cardiac antigen recognition.[25] Impaired IRE1α activation and reduced Xbp1s expression shift infiltrating T cells toward a more inflammatory phenotype with elevated expression of IFN-γ and IL-4, contributing to adverse cardiac remodeling.[25]

A model of immune dysregulation comprising genetic and acquired risk factors was proposed in the pathogenesis of HFpEF.[26] Genetic inactivating mutations in hematopoietic stem cells of genes, such as *DNMT3A*, *TET2*, *ASXL1*, and *JAK2*, linked to clonal hematopoiesis of indeterminate potential, are associated with development of HFpEF in animal models, and with immune dysregulation and risk of HF hospitalization in patients.[26] These inactivating mutations stimulate the clonal expansion of proinflammatory myeloid cells (e. g., monocytes, macrophages), and T cells with a higher Th17/T reg ratio, contributing to the rise of a proinflammatory hematopoietic phenotype.[24] Thus, cardiometabolic HFpEF comorbidities, including hypertension, obesity, and diabetes, lead to recruitment of these already stimulated immune cells, including $CCR2^+$ monocytes, Th1, and Th17 cells.[26] Genetically mediated immune predisposition (clonal hematopoiesis of indeterminate potential mutations) may skew immune cells toward a proinflammatory phenotype and modulate the individual inflammatory response to cardiovascular stressors toward HFpEF. Further investigations are needed to elucidate the role of clonal hematopoiesis of indeterminate potential mutations as a genomic biomarker for HFpEF.

Patients with HFpEF often exhibit a pronounced neutrophil-driven inflammatory phenotype, characterized by elevated circulating neutrophils and increased neutrophil extracellular trap (NET) markers, such as cell-free double-stranded DNA, elastase-2, and citrullinated histone H3.[27] Clinically, peak NET marker levels are particularly pronounced during episodes of decompensated HFpEF.[28] In the SAUNA HFpEF mouse model, generated with a combination of salted drinking water, unilateral nephrectomy, and chronic aldosterone infusion, cardiac tissue showed marked neutrophil infiltration and NET deposition, which correlated with diastolic dysfunction, inflammation, macrophage recruitment, and fibrosis.[27] Pharmacological disruption of NET formation, via DNase (deoxyribonuclease) 1 or empagliflozin, attenuated NETosis, reduced myocardial inflammation and fibrosis, and ameliorated diastolic performance.[27]

VASCULAR CELL DYSFUNCTION IN HFpEF

The endothelium lines all vessels and hence constantly interacts with hemodynamic forces, the coagulation system, and the immune-metabolic milieu. All risk factors for HFpEF impair vascular function (ie, dysfunction is intended as any detrimental modification of the endothelial phenotype) and contribute to the pathophysiology of HFpEF. Meta-inflammation causes a systemic dysfunctional vasodilation as well as coronary microvascular dysfunction, which is characterized by impaired coronary flow reserve and structural abnormalities of the coronary tree. Coronary microvascular dysfunction causes an inadequate myocardial perfusion reserve, leading to areas of chronic latent myocardial ischemia, which, in turn, activates proimmunoinflammatory and pro-oxidative mechanisms and sustains a detrimental vicious cycle in HFpEF.[29]

After the endothelial-mediated recruitment of immune cells due to the increased expression of adhesion molecules, high oxidative stress and iNOS (inducible NO synthase)-induced nitrosative stress lead to reduced NO bioavailability due to lower arginine substrate, eNOS (endothelial NO synthase) activity, and endothelial p-53–induced senescence.[30] Vasoconstriction becomes predominant due to increased resting endothelin-1-mediated vasoconstriction and smooth muscle cell contractile activation.[31] Endothelial proinflammatory and dysfunctional maladaptation (including high NADPH oxidase 2 expression and eNOS uncoupling) are documented in animal models (eg, ZSF1 [Zucker fatty and spontaneously hypertensive]-HFpEF rats) and human HFpEF specimens, influencing via paracrine signals adjacent cardiomyocytes (ie, leading to reduced myocardial nitrite/nitrate concentration, cyclic guanosine monophosphate content, and protein kinase G activity) and the extracellular matrix, predisposing fibroblasts to activation patterns promoting hypertrophy, fibrosis and high diastolic stiffness.[32] For instance, cardiomyocytes became more susceptible to pressure overload-induced HF in a

transverse aortic constriction model as a consequence of endothelial alterations of energetic metabolism (ie, disrupted glucose transport from ECs to cardiomyocytes), due to impaired endothelial SIRT (sirtuin) 3/apelin signaling.[33] In patients with diabetes with HFpEF, SIRT6 activation, via PPARγ reduction, inhibited endothelial FA uptake, resulting in lower fatty acid translocation across ECs. Furthermore, a blunted endothelial SIRT6 expression was associated with decreased cardiac lipid accumulation, which is a hallmark of HFpEF progression in T2DM.[34]

In turn, ECs are profoundly influenced by signaling molecules characterizing the HFpEF milieu. Angiopoietin-like 4 secreted by cardiac fibroblasts exerts antiangiogenic functions leading to microvascular and capillary rarefaction, as recently described at single-cell resolution in the 2-hit HFpEF mouse model.[35] Angiopoietin-like 4, which is barely expressed in control fibroblasts, becomes highly induced in HFpEF, possibly constituting an important stress indicator in fibroblasts in HFpEF.

Single-cell transcriptomics is enabling a deeper characterization of fibroblast activation patterns in HFpEF. Specific fibroblast signatures include markers of metabolic stress, basement membrane genes, and activation of proinflammatory pathways, which are distinct from those seen in a murine model of HF with reduced ejection fraction (HFrEF; eg, induced by Ang II administration) or adverse remodeling seen after myocardial infarction. Interestingly, the latest evidence in HFpEF points to the differentiation of cardiac fibroblasts toward matrifibrocytes, which are a specialized type of cardiac fibroblast, characterized by the expression of Cartilage Intermediate Layer Protein, an ECM (extracellular matrix) protein. Matrifibrocytes emerge during chronic stress conditions and contribute to cardiac fibrosis with characteristic collagen I deposition. Matrifibrocytes have been recently observed as a predominant feature in HFpEF, whereas little expression of FAP (fibroblast activation protein), which is a marker for myofibroblast activation in cardiac fibrosis, has been reported. Conversely, high expression of FAP, suggesting a predominant myofibroblast activation, has been described in the HFrEF model achieved with angiotensin II administration or after myocardial infarction.[36] The localization of these different fibroblast clusters within the heart and to which extent these fibroblast phenotypes are conserved in human hearts with HFpEF need further elucidation.

Stress-induced release of cardiomyocytes-derived extracellular vesicles sampled at the coronary level has been associated with markers of HFpEF functional severity (eg, NT-proBNP [N-terminal pro-B-type natriuretic peptide] levels and echocardiographic parameters reflecting elevated filling pressure),[37] however, whether and how these extracellular vesicles may modify EC homeostasis and secretome remain to be defined.

Pericytes, which are the mural cells of the capillaries, communicate with ECs by either direct contact or by paracrine signaling and play a prominent role in controlling the cardiac vascular-myocyte microenvironment. Pericyte dysfunction precedes the onset of microvascular and diastolic dysfunction and contributes to the derangement of EC biology in HFpEF.[38] In volume overload–dependent on high salt-induced renal dysfunction in db/db mice, dysfunctional pericytes induced remodeling of coronary blood vessels, both in the microvascular and macrovascular niche. The detrimental remodeling was mediated by TNFa-STAT1–dependent paracrine signaling and was characterized by thickening and vessel enlargement, increase in capillary dilatation, reduced pericyte proliferation with capillary detachment, and density loss.[39] Recently, alterations of lymphatic ECs (ie, lower density and impaired lymphangiogenic capacity) and structural abnormalities of cardiac lymphatic vessels, such as a reduction in lymphatic volume, discontinuous and fragmented vessels, and impaired lymphatic drainage of interstitial fluid and inflammatory cells, have been described in the 2-hit mouse model of HFpEF.[40] Similar defects of the cardiac lymphatic were confirmed in myocardial biopsies from patient with HFpEF. Mechanistically, the pathological inhibition of lymphangiogenic responses in lymphatic ECs was linked to the defective catabolism of branched-chain amino acids (valine, leucine, and isoleucine degradation) and altered glucose metabolism. These lymphatic abnormalities were detected in mice before the onset of diastolic dysfunction and decreased exercise capacity, suggesting a pathogenic role deserving further investigation. Interestingly, the specific reactivation of lymphangiogenesis achieved via VEGF (vascular endothelial growth factor)-mediated VEGF receptor 3 selective activation restored the cardiac lymphatic function and structure in HFpEF, significantly ameliorating cardiac hypertrophy, fibrosis, edema, and inflammation.[39]

IMMUNOMETABOLIC MECHANISMS IN HFpEF

From Metabolism to Inflammation: Immunometabolism and Immunometabolic Crosstalk

Although immune cell–mediated direct damage to the myocardium is well-studied, metabolic crosstalk between inflammatory cells and cardiac muscle remains poorly understood. Cellular and systemic metabolic derangements influence immune responses, creating a bidirectional crosstalk that is emerging as a critical component of the pathogenesis of several cardiometabolic diseases, including HFpEF. Immunometabolism refers to this condition and highlights the interplay between changes in systemic and tissue metabolism with the modulation of

immune cell reprogramming under physiological and pathological conditions.[41]

Within the heart, activated immune cells from metabolic stress infiltrate inflamed tissue and adapt to the local microenvironment (oxygen tension, acidification, and the presence of metabolites) by undergoing further metabolic reprogramming.[3] For instance, immune cells stabilize the transcription factor HIF1α (hypoxia-inducible factor 1α) in response to a decrease in oxygen availability. HIF1α induces the transcription of anabolic genes for glycolysis and mitochondrial metabolism in T cells and macrophages.[3] The resulting highly glycolytic activated immune cells produce lactate, which impairs the motility of $CD4^+$ and $CD8^+$ T cells, thereby trapping them at inflammatory sites and preventing inflammation resolution.[3] Among proinflammatory metabolites, succinate might also be a potential candidate in sustaining immunometabolic crosstalk and inflammation in HFpEF. Dendritic cells exposed to succinate increase TNF-α and IL-1β expression.[42] The latter further enhances succinate receptor 1 expression in macrophages, fueling a potential proinflammatory cycle in the induction and maintenance of inflammation and adverse remodeling in HFpEF.[3]

Metabolic disruption leads to the systemic accumulation of endogenous metabolites or danger signals, which subsequently activate the NLRP3 (NOD-, LRR- and pyrin domain-containing protein 3) receptor and drive inflammation.[41] NLRP3 is a cytosolic pattern recognition receptor recognizing damage-associated molecular patterns and pathogen-associated molecular patterns to initiate the NLRP3 inflammasome. The NLRP3 inflammasome acts as a critical sensor of metabolic stress and is activated by excess nutrients, lipids, and oxidative stress, linking metabolic disturbances to the activation of inflammatory responses. Moreover, it promotes a transient IL-1β release, which facilitates postprandial insulin secretion and glucose regulation metabolism.[43] However, the persistent activation of the NLRP3 inflammasome-IL-1β pathway during chronic inflammation related to metabolic disturbances contributes to the exhaustion of the insulin secretion mechanisms. Serum NLRP3 and IL-1β levels are significantly higher in patients with HFpEF than in patients with HFrEF and are closely related to diastolic dysfunction.[44] In the 2-hit HFpEF model, the inhibition of NLRP3 inflammasome with a specific small-molecule inhibitor (MCC950) reduced myocardial hypertrophy and fibrosis, improved LV diastolic function, exercise intolerance, and glucose intolerance.[44] Moreover, inhibition of NLRP3 inflammasome in mice ameliorates cardiac function and blood pressure, improves lipid metabolism abnormalities, and inhibits pyroptosis in cardiomyocytes.[45]

The heterogeneity of immunometabolic response in HFpEF may explain the variable presence of myocardial fibrosis and hypertrophy. Individuals with advanced metabolic dysfunction and visceral adiposity may have stronger, systemic, and sustained inflammatory burden, and in turn, stronger immunometabolic activation. In these patients, highly glycolytic activated immune cells release TGF-β and IL-6 that activate fibroblasts and hypertrophic pathways. Conversely, in patients with moderate metabolic dysfunction, immune activation may be localized in the microvasculature, impairing endothelial NO signaling with microvascular dysfunction and, in turn, diastolic dysfunction, but without engaging fibroblast or cardiomyocyte remodeling pathways. This may explain why some patients do not display cardiac hypertrophy or fibrosis. Thus, the differences in immune-metabolic activation profiles, influenced by comorbidities and adipose–immune–cardiac interactions, may underlie the phenotypic diversity in HFpEF.

DISRUPTED LIPID METABOLISM IN HFpEF

The heart primarily uses FAs derived from circulating lipoproteins (chylomicrons, VLDL [very-low-density lipoprotein], and albumin-bound FAs for energy.[46] LpL (lipoprotein lipase) catalyzes hydrolysis of triglyceride-rich lipoproteins at the EC surface, while the scavenger receptor CD36 mediates the transport across the EC barrier. Genetic deletion of CD36 or LpL or overexpression of the LpL inhibitor Angptl4 (angiopoietin-like 4) leads to defective lipid uptake and cardiac dysfunction.[47] In HFpEF, adiposity is linked to worsening cardiac function, with excessive influx of FAs leading to the accumulation of lipotoxic species in the myocardium, such as diacylglycerols, triacylglycerols, and ceramides.[46] Lipid intermediates upregulate NADPH oxidase via activation of protein kinase C, resulting in an increase in reactive oxygen species content.[48]

Lipotoxicity directly affects cardiac metabolism, resulting in loss of metabolic flexibility followed by cardiac ATP depletion, functional impairment, and diastolic dysfunction.[46] Moreover, it impairs cellular homeostasis and disrupts tissue function through multiple mechanistic models, including alterations of immune responses such as macrophage polarization to a proinflammatory phenotype or immune cell epigenetic reprogramming.[46]

Cardiac lipotoxicity is more relevant when specific lipid classes accumulate in the heart. Although oleic acid is not deleterious,[49] palmitic acid is more cytotoxic via (1) impairing mitochondrial function, disrupting energy production, and increasing reactive oxygen species generation, and (2) promoting myocardial inflammation via direct binding to the TLR4 accessory protein MD2, (3) inducing a direct cellular damage leading to impaired contractility.[50–52]

The disruption of the Xbp1s-FoxO1 (forkhead box O1) signaling axis is recognized as a crucial regulator of lipid metabolism and cardiac function in HFpEF. Indeed, nitrosative stress from systemic inflammation suppresses the Xbp1s (spliced form of the X-box-binding protein-1)

arm of the unfolded protein response, contributing to the development of myocardial steatosis in HFpEF.[53] Downstream effect of inhibition of the Xbp1s branch results in STUB1 suppression, and FoxO1 stabilization and hyperactivation in cardiomyocytes, which promotes cardiomyocyte steatosis and related adverse outcomes.[53] FoxO1 hyperactivation further promotes the transcriptional expression of proinflammatory molecules, including TLR1 (toll-like receptor 1), TLR4, IL-1β, and TNF-α, which in turn trigger an immune system response.[54]

Likewise, the accumulation of free cholesterol promotes cell lipotoxicity. Although the LDLR (low-density lipoprotein receptor) is expressed at very low levels in the heart, and therefore it is unlikely that HF could develop as a consequence of increased LDL (low-density lipoprotein) cholesterol accumulation, other receptors, such as CD36 or the VLDLR (VLDL receptor), can mediate remnant lipoproteins internalization in the heart.[55] VLDLR was shown to be upregulated under ischemic conditions and to contribute to heart lipoprotein uptake and cardiac lipotoxicity.[55] Similarly, increased cardiac expression of CD36, as a consequence of PCSK9 deficiency, was associated with increased heart cholesterol content.[56] Interestingly, PCSK9-deficient mice on chow diet and subjects with a loss-of-function mutation of PCSK9 develop HFpEF, whereas lower plasma LDL cholesterol levels may increase adiposity and epicardial fat deposition.[56,57]

Cholesterol not only acts as a structural molecule but also affects cardiometabolic inflammation, by modulating lysosomal function, NLRP3 sensing, and mitochondrial dynamics, among others.[58,59] Moreover, apoE deficiency, promotes increased CD4+T effector memory cell activation that might contribute to increased inflammation and the HFpEF-like phenotype [60,61]

These findings highlight the crosstalk between immunity, metabolism, and the heart. Indeed, lipid accumulation in visceral adipose tissue and particularly in epicardial adipose tissue is strongly associated with the risk of HFpEF.[62] Expanded visceral adipose tissue acts systemically, while the epicardial adipose tissue secretome, composed of leptin, TNF-α, IL-1β and IL-6, and resistin, is readily transmitted to the underlying myocardium, perpetuating and sustaining a chronic inflammatory response with immune activation.[63] Accumulation of epicardial adipose tissue is associated with the hallmark features of HFpEF, such as myocardial fibrosis, ventricular hypertrophy, and increased cardiac filling pressures.[63]

Interestingly, in T2DM, impaired insulin signaling increases circulating free FA as a result of increased lipolysis. This contributes to increased myocardial FA utilization, while cardiac glucose uptake and oxidation are reduced in T2DM despite hyperglycemia; however, it remains debated whether these changes are adaptive or maladaptive.[64] In hyperglycemic mice with inducible cardiomyocyte-specific expression of GLUT4, enhanced myocardial glucose in nondiabetic mice decreased mitochondrial ATP generation and was associated with echocardiographic evidence of diastolic dysfunction. These findings suggest that reduced glucose utilization in diabetic cardiomyopathy might protect against glucotoxicity.[65]

THERAPEUTIC STRATEGIES TARGETING CARDIOMETABOLIC RISK IN HFpEF

Throughout the last decade, randomized clinical trials expanded guideline-directed medical therapies for the management of HFpEF, providing new evidence with important prognostic implications. In addition to the various beneficial immunomodulatory effects of lifestyle interventions in HFpEF management,[66] emerging evidence indicates that contemporary evidence-based HFpEF therapeutics also influence immunometabolic pathways and exert anti-inflammatory effects, beyond their established benefits on hemodynamics and cardiac energy metabolism (Figure 2).

SODIUM-GLUCOSE COTRANSPORTER 2 INHIBITORS

Although initially developed as antihyperglycemic agents, SGLT2 (sodium-glucose cotransporter 2) inhibitors have become a cornerstone of guideline-directed management of HFpEF. Besides their benefits on metabolic end points, the use of SGLT2 inhibitors substantially reduced cardiovascular mortality and HF events, and improved health-related quality of life (HRQL) in patients with symptomatic HF and LV ejection fraction ≥40%.[67] Although exact underlying mechanisms beyond their effects on diuresis and natriuresis remain to be further elucidated, treatment benefits with SGLT2 inhibitors are thought to exert improvements in LV remodeling and function by attenuating cardiac energy metabolism, mitigating meta-inflammation, and limiting cardiac fibrosis. In the validation cohort of the EMPEROR-Preserved trial, large-scale proteomic analyses affirmed SGLT2 inhibitors to promote autophagy, restore mitochondrial health and ATP production, promote iron mobilization and erythropoiesis, influence renal tubular ion reabsorption, and normalize cardiac and renal structure.[68] Key mediators of these benefits with SGLT2 inhibitors may include the upregulation of nutrient deprivation signaling, downregulation of nutrient surplus signaling, an increased expression and activity of AMPK (AMP-activated protein kinase), SIRT1, SIRT3, SIRT6, and PGC1-α (peroxisome proliferator–activated receptor γ coactivator 1-α) and decreased activation of mTOR (mammalian target of rapamycin) in diverse tissues, with direct molecular effects on ECs, adipose tissue, and immune cells, limiting

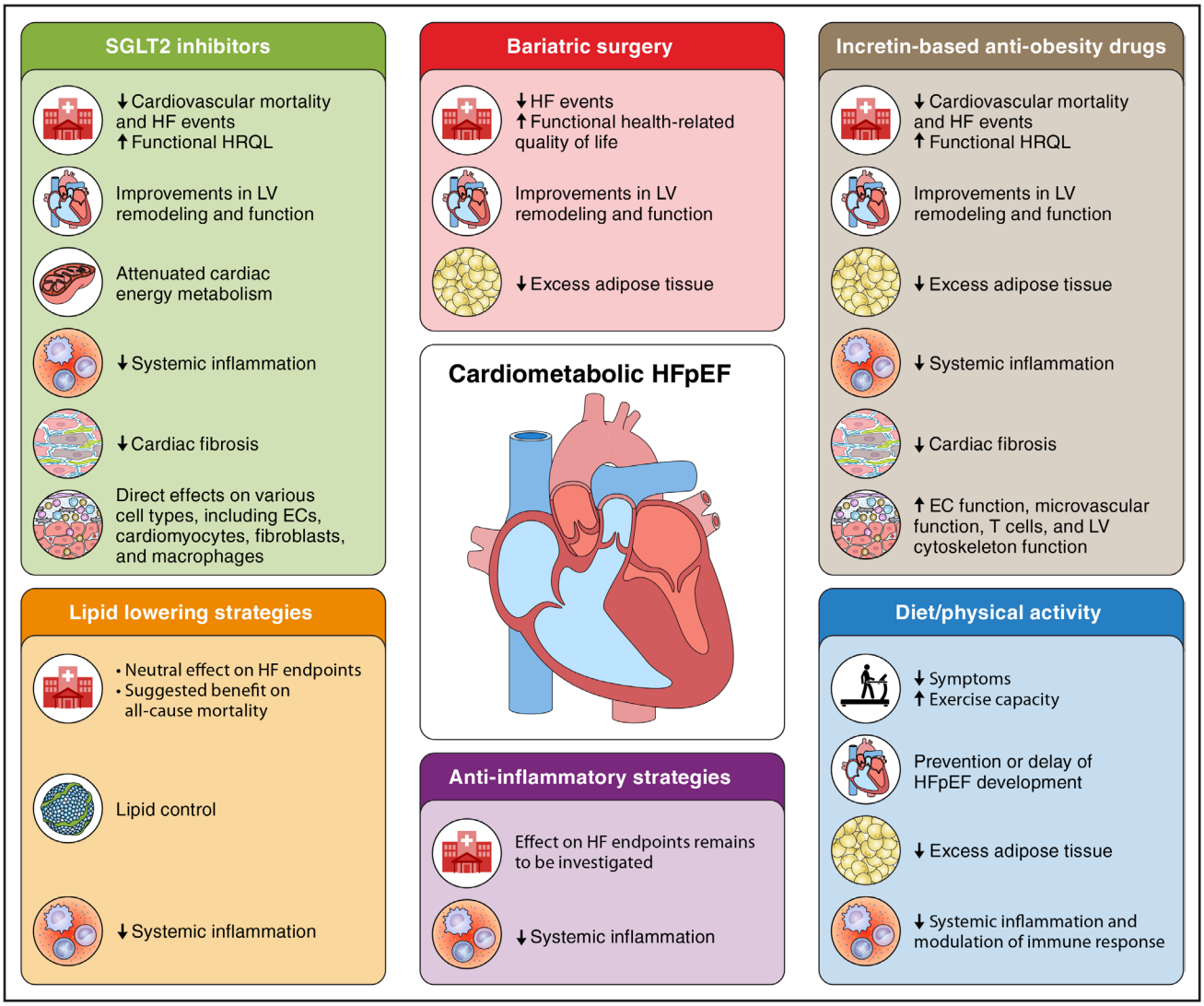

Figure 2. Pharmacological and nonpharmacological strategies targeting cardiometabolic risk in heart failure with preserved ejection fraction (HFpEF).
EC indicates endothelial cell; HF, heart failure; HRQL, health-related quality of life; LV, left ventricular; and SGLT2, sodium-glucose cotransporter 2.

downstream proinflammatory and profibrotic pathways.[69] As such, meta-analyses of randomized clinical trials indicate SGLT2 inhibitors reduce epicardial adipose tissue and beneficially modulate adipokine signaling, with increased adiponectin release and reduced secretion of leptin, resulting in attenuated neurohormonal activation, sodium retention, microvascular rarefaction, cardiac fibrosis, and inflammation.[70,71] In preclinical models, SGLT2 inhibitors decreased plasma levels of systemic inflammation, such as CRP (C-reactive protein), TNF-α, and IL-6, with key anti-inflammatory properties involving the modulation of macrophage-mediated inflammation.[72] Likewise, SGLT2 inhibitors were shown to attenuate NLRP3 inflammasome activation in macrophages, which may be in part mediated by the increase of ketone metabolites and decreased uric acid levels, leading to decreased macrophage infiltration and cytokine release.[73] Moreover, SGLT2 inhibitors may inhibit macrophage-mediated differentiation of monocytes to macrophages, promoting the polarization of macrophages from a proinflammatory M1 phenotype to an anti-inflammatory M2 phenotype.[61] In vitro models of CD80+ macrophages suggest that the SGLT2 inhibitors empagliflozin and gemigliptin may further reduce inflammation through downregulation of the IKK/NF-κB (nuclear factor-κB), MKK7/JNK, and JAK2/STAT1 pathway.[74] Consistent with the evidence from contemporary HFpEF trials, data from the EMPA-REG OUTCOME trial suggest direct effects on human cardiac myofibroblasts through reductions in myofibroblast activity and modulation of collagen remodeling.[75] Ex vivo single-cell sequencing data of human cardiac tissue from patients with HF further demonstrated that SGLT2 inhibitor treatment is associated with specific antifibrotic gene expression patterns in fibroblasts.[76] Mouse models

of HFpEF similarly indicate that SGLT2 inhibitors may also attenuate hypertrophy, fibrosis, and autophagy by favorably modulating the crosstalk between macrophages and cardiomyocytes through anti-inflammatory effects resulting from limited inflammatory gene expression in resident cardiac macrophages.[61] Similarly, SGLT2 inhibitors have been shown to directly affect vascular cells by favorably regulating the proliferation, migration, differentiation, survival, and senescence of ECs, increasing the bioavailability of endothelium-derived NO, together with antioxidant and anti-inflammatory effects mediated by decreasing the endothelial expression of adhesion molecules, proinflammatory cytokines, and chemokines, and elevated adiponectin expression.[77]

INCRETIN-BASED OBESITY MANAGEMENT THERAPEUTICS

Over the past decade, incretin-based obesity management therapeutics have emerged as a key therapeutic strategy for managing T2DM, and obesity. Alongside the considerable weight loss observed with GLP-1 (glucagon-like peptide-1) and combined GLP-1/GIP (glucose-dependent insulinotropic polypeptide) receptor agonists, recent randomized trials further demonstrated substantial improvements in clinical outcomes and HRQL in patients with obesity-related HFpEF.[78,79] Notably, reductions in markers of systemic inflammation observed with both GLP-1 and combined GLP-1/GIP receptor agonism in the SELECT, STEP-HFpEF program, and SUMMIT trials, supported by experimental and clinical evidence of an attenuated immune response with incretin-based obesity management drugs, suggest additional metabolic benefits beyond weight reduction. As such, key anti-inflammatory effects of incretin-based obesity management drugs are reflected by reductions in CRP, TNF-α, IL-6, MCP-1 (monocyte chemoattractant protein-1), and MMP-9 (matrix metalloproteinase-9) levels, with underlying immunomodulatory mechanisms.[80] Underlying immunomodulatory mechanisms of incretin-based drugs include suppressed macrophage secretion of inflammatory cytokines, inhibitory effects on local and systemic T-cell–driven inflammation, attenuation of TLR (toll-like receptor) agonist-induced inflammatory activity, and reduction of proinflammatory signaling in adipose tissue and subsets of central nervous system neurons.[80] Preclinical data further suggest improvements in cardiac fibrosis, EC function, and microvascular function as potential mechanisms explaining the therapeutic benefits of incretin-based obesity management drugs.[81,82] Transcriptomic and proteomic analyses of HFpEF mouse models further indicate that GLP-1 receptor agonism may improve LV cytoskeleton function, oxidative stress, and restore protective immune responses in visceral adipose tissue.[83] Although reductions in adverse cardiovascular events are thought to be predominantly driven by direct tissue effects, weight loss may largely account for improvements in osteoarthritis, obstructive sleep apnea, and metabolic dysfunction-associated steatohepatitis.[84] Consistent with the proposed prognostically relevant role of direct tissue effects, observational data of patients with HFpEF with T2DM from the TriNetX research network recently suggested that the benefits of incretin-based obesity management drugs on clinical outcomes and surrogates of metabolic dysregulation may extend even to patients without obesity.[85] Despite the meaningful clinical benefits, ongoing and future studies need to elaborate on a more comprehensive mechanistic understanding of the benefits of incretin-based therapeutics in HFpEF.

BARIATRIC SURGERY

The long-term follow-up after bariatric surgery, spanning over 30 years, has documented multiple cardiometabolic benefits such as T2DM remission, maintenance of glycemic control, decrease of microvascular and macrovascular diabetic complications, as well as overall and cardiovascular mortality.[86] Bariatric surgery in HFpEF is associated with improved symptoms and lower hospitalization costs compared with patients with obesity with HFpEF without bariatric surgery.[87] At the cardiac level, decreases in LV mass and relative wall thickness, along with improvements in myocardial stiffness, diastolic function, and left atrial filling pressure as determined by echocardiography have been reported; however, these studies are scarce, often included few patients with both HFpEF and HFrEF, who were followed up for short time periods.[88] Mechanistic insights are lacking to elucidate whether body weight loss and the systemic increase in circulating GLP-1 concentrations after bariatric surgery play a primary role, or whether the observed benefits may be mediated by additional mechanisms involving other gut hormones or mediators of the entero-cardiac axis.

IMPACT OF LIPID-LOWERING THERAPIES ON HFpEF

The use of lipid-lowering therapies in patients with HF is controversial. While in patients without HF, statins as well as their combination with other lipid-lowering therapies reduce atherosclerotic cardiovascular disease risk, including HF-related events, no additional benefit was seen in statin-treated patients with HF (CORONA and GISSI-HF).[89,90] Yet, systemic reviews and meta-analyses suggest a reduction in all-cause mortality in patients with HFpEF on statin therapy.[91] Data on the impact of other lipid-lowering therapies on HFpEF are lacking, suggesting the need to further investigate whether lipid-lowering therapies could have a benefit or are neutral in the context of HFpEF.

TARGETED ANTI-INFLAMMATORY THERAPEUTICS

Although inflammation may play a central role in the pathophysiology of HFpEF, contemporary evidence from randomized clinical trials on the effect of anti-inflammatory interventions in HFpEF remains sparse. In the DHART trial of 12 patients with HFpEF with CRP >2 mg/L, IL-1 blockade with the recombinant human receptor antagonist anakinra for 14 days reduced systemic inflammatory response and improved aerobic exercise capacity, whereas in the DHART2 trial of 31 patients with HFpEF with CRP >2 mg/L, treatment with anakinra for 12 weeks did n0t improve cardiorespiratory fitness despite greater reductions in CRP levels and NT-proBNP.[92,93] However, given the small sample sizes and the differences in the enrolled populations, the role of anakinra for the treatment of HFpEF remains unclear. A prespecified exploratory analysis of the CANTOS trial suggested that interleukin-1β inhibition with canakinumab is related to a dose-dependent reduction in HF hospitalizations and the composite of HF hospitalizations or HF-related mortality in patients with prior myocardial infarction and elevated high-sensitivity CRP.[94] Given the exploratory, hypothesis-generating nature and the inability to differentiate the effects of canakinumab on HF with reduced compared with preserved LV function due to unavailable data on LV ejection fraction at randomization or at the time of HF hospitalization in the CANTOS trial, the role for IL-1β inhibition in HFpEF needs to be further evaluated. In the phase 2a SATELLITE trial of 41 patients with symptomatic HF with LV ejection fraction ≥40%, the myeloperoxidase inhibitor AZD4831 (mitiperstat) showed a favorable safety profile and target inhibition, with a trend toward improved HRQL.[95] Further trials need to confirm whether AZD4831 may decrease symptoms and improve functional capacity and HRQL in patients with HFpEF. Although the efficacy of methotrexate in HFpEF remains to be evaluated by a randomized clinical trial, a retrospective cohort study of patients with rheumatoid arthritis performed at the Vanderbilt University Medical Center reported a lower risk of incident HFpEF with methotrexate, compared with matched controls.[96]

FUTURE DIRECTIONS

Despite recent therapeutic progress with SGLT2 inhibitors and incretin-based drugs, patients with HFpEF remain at increased risk. Whereas current evidence-based therapeutics together with optimal comorbidity management may reduce disease progression, key features of cardiac remodeling and immunometabolic dysregulation as part of the HFpEF syndrome may not be entirely reversible. Considerable sex disparities persist due to potential sex-specific differential responses to HF therapeutics, gaps in sex representation between HF-, cardiovascular-, and obesity outcome trials, and insufficient knowledge about sex-specific immunometabolism mechanisms from preclinical studies, collectively underscoring the need to better address sex differences in future studies.[97] Given the elevated burden and prognostic impact of cardiometabolic impairments and their systemic implications, the development of targeted approaches addressing hallmarks of cardiometabolic impairments, including inflammation, immune dysregulation, adverse cardiac remodeling, and cardiac fibrosis may hold promise. Studies evaluating systemic anti-inflammatory agents in HFpEF comprise the COLpEF trial (URL: https://www.clinicaltrials.gov; Unique identifier: NCT04857931) of colchicine and the ongoing HERMES trial (URL: https://www.clinicaltrials.gov; Unique identifier: NCT05636176) currently investigating a novel monoclonal antibody targeting IL-6. Mitigating inflammation, oxidative stress, and microvascular dysfunction through myeloperoxidase inhibition is currently evaluated in a phase 2a trial of patients with HFpEF (URL: https://www.clinicaltrials.gov; Unique identifier: NCT03756285). Moreover, adrecizumab, a monoclonal, non-neutralizing antibody stabilizing adrenomedullin to improve endothelial dysfunction is currently assessed in a phase 2a trial of patients hospitalized for HF (URL: https://www.clinicaltrials.gov; Unique identifier: NCT04252937). The ongoing phase 2a REGRESS-HFpEF trial (URL: https://www.clinicaltrials.gov; Unique identifier: NCT02941705) evaluates the effect of intracoronary administration of cardiosphere-derived cells on proinflammatory and profibrotic signaling, functional status, exercise haemodynamics, and myocardial fibrosis in patients with HFpEF. Additional experimental strategies to mitigate cardiometabolic inflammation may include genetic or antibody-based CCR2 modulation approaches.[98] Last, targeting cardiac fibrosis by altering TGF-β signaling may reverse cardiac remodeling sustained by maladaptive fibroblast activation, with promising early phase clinical trial data from emerging epigenetic regulators such as small molecule agents (URL: https://www.clinicaltrials.gov; Unique identifier: NCT02932566) and microRNA-based therapeutics (URL: https://www.clinicaltrials.gov; Unique identifier: NCT04045405).[99,100]

CONCLUSIONS

Cardiometabolic comorbidities are central features in the pathophysiology of HFpEF, driving its development and disease progression, characterized by persistent chronic immuno-inflammatory state and immune system dysregulation. The chronic systemic proinflammatory state impairs vasodilation and causes endothelial coronary microvascular dysfunction. Cellular and systemic metabolic derangements create a bidirectional crosstalk between systemic and cardiac tissue metabolism, sustaining a vicious cycle of cardiac chronic inflammatory response, with the NLRP3

inflammasome playing a pivotal role as a critical sensor of metabolic stress. The activation of both the innate and adaptive immune cells in cardiac tissue promotes inflammation and fibrosis, impairing cardiac relaxation and compliance. Contemporary HFpEF trials demonstrated that targeting cardiometabolic risk with SGLT2 inhibitors and incretin-based obesity management drugs improves clinical outcomes, HRQL, and markers of meta-inflammation. Further efforts aiming to distinguish the different subtypes of infiltrating immune cells, as well as their functions and implied pathways, must be done to consider new potential immunomodulatory therapeutic strategies.

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Received May 5, 2025; accepted January 13, 2026.

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Sources of Funding

This work did not receive any specific funding from public or private entities, commercial, or institutional sources, nor any substantial contributions from individuals.

Disclosures

Dr Peikert has received a research grant from the German Research Foundation. Dr Schiattarella was supported by DZHK (German Center for Cardiovascular Research–81X3100210; 81X2100282); the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation–SFB-1470–A02; SFB-1470–Z01), and the European Research Council (ERC) StG 101078307. Dr Norata was supported by Nanokos (European Commission Ref EUROPEAID/173691/DD/ACT/XK), PNRR Missione 4 (Progetto CN3–National Center for Gene Therapy and Drugs based on RNA Technology), PNRR Missione 4 (Progetto MUSA [Multilayered Urban Sustainability Action]), PNRR Missione 6 (PNRR-MAD-2022–12375913), CARDINNOV, Ministry of Research and University under the umbrella of the Partnership Fostering a European Research Area for Health (ERA4Health; GA No. 101095426 of the EU Horizon Europe Research and Innovation program), Ministry of Research and University (PRIN 2022 7KTSAT). The continued financial support by the Swiss National Science Foundation PRIMA: PR00P3_179861/1 and the Swiss Life Foundation, the Heubergstiftung, the Philhuman Stiftung, the Novartis Foundation, and the Swiss Heart Foundation, Switzerland to Dr Osto. The other authors report no conflicts.

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