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Inflammatory Pathways and Their Implications in Heart Failure With Preserved Ejection Fraction

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Introduction

Heart failure with preserved ejection fraction (HFpEF) is a complex syndrome characterized by elevated left ventricular (LV) stiffness and filling pressures, despite normal or near-normal EFs. It accounts for approximately half of all HF cases and has become increasingly prevalent with an aging population.[1] In contrast to HF with reduced EF, HFpEF is less understood, and options for effective treatment are limited.[2] Recent evidence suggests that systemic inflammation plays a pivotal role in HFpEF pathophysiology.[3]

Current Limitations

Historically, the pathophysiologic mechanisms of HFpEF have been attributed primarily to diastolic dysfunction and abnormal ventricular-arterial coupling.[4] This paradigm falls short, however, in explaining the full spectrum of clinical manifestations of HFpEF. Although inflammation's role in HFpEF has been increasingly recognized, the understanding of the mechanistic link between systemic inflammation and the development of HFpEF is still limited. Much of the current understanding is derived from observational studies, which have shown elevated inflammatory markers, such as C-reactive protein, tumor necrosis factor α, and interleukin-6 (IL-6), in patients with HFpEF.[5] The precise pathways through which inflammation contributes to the development and progression of HFpEF have yet to be fully elucidated, however, presenting a significant limitation in the current research landscape.

One key route by which systemic inflammation can lead to diastolic LV stiffness, a hallmark of HFpEF, is through the deposition of collagen, a crucial event in fibrosis.[5] Systemic inflammation triggers the expression of vascular-cell adhesion molecules, which recruit monocytes that transform into macrophages. These macrophages secrete transforming growth factor β, stimulating myofibroblasts to deposit collagen, thereby contributing to ventricular stiffness.[6]

In addition, systemic inflammation is associated with alterations in the protein titin, a critical player in the myocardial contractile apparatus. Studies in HFpEF models and human myocardial biopsies have shown that systemic inflammation, characterized by the presence of tumor necrosis factor α, IL-1β, and IL-6, is associated with lower endothelial production of nitric oxide as well as decreased activity of soluble guanylate cyclase and protein kinase G in cardiomyocytes.[2] These changes reduce titin phosphorylation and promote the formation of disulfide bonds within titin, leading to its rigidification and contributing to diastolic LV stiffness.[3]

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Another proposed pathway of systemic inflammation in HFpEF involves the unfolded protein response. Systemic inflammation is known to upregulate inducible nitric oxide synthase, which subsequently reduces levels of spliced χ-box binding protein 1 and suppresses the expression of proteins involved in the unfolded protein response. This suppression could lead to an accumulation of destabilized proteins, similar to the accumulation observed in amyloidosis.[7]

These interconnected pathways involving inflammation, fibrosis, and protein modification offer promising avenues for research. Without a more detailed understanding of these processes, however, the development of targeted therapies to modulate inflammation and its effects in HFpEF remains challenging.

Recent Developments

Emerging research into the role of systemic inflammation in HFpEF has led to promising developments in targeted therapeutic approaches. Moreover, clinical trials investigating anti-inflammatory therapies have begun to show some promise. The CANTOS trial, targeting IL-1β, resulted in a significant reduction in hospitalizations because of HF, including HFpEF.[7] The effects were notably observed when canakinumab successfully lowered high-sensitivity C-reactive protein below 2 mg/L.

Interleukin-6 is another inflammatory cytokine that has been proposed as a therapeutic target in HFpEF. It not only mediates hepatic C-reactive protein production but also contributes to volume expansion and diuretic resistance by activating the epithelial sodium channel and impairing natriuresis.[8] Evidence suggests that IL-6 blockade (eg, with the monoclonal antibodies tocilizumab or ziltivekimab) could restore cardiomyocyte titin phosphorylation, reduce myocardial fibrosis, and reverse LV hypertrophy.[8]

Sodium-glucose cotransporter-2 (SGLT2) inhibitors have also been shown to reduce hospitalization in patients with HFpEF, and there is growing evidence of their anti-inflammatory effects, which have largely been attributed to the systemic and metabolic improvements associated with their glucosuric effects.[9] Their cardiovascular benefits appear to extend beyond glucose control and reduced glucotoxicity, suggesting that additional mechanisms may be at play. For instance, SGLT2 inhibitors have been shown to lower uric acid levels, potentially mitigating oxidative stress by promoting antioxidant SIRT1 expression or by directly inhibiting heart-specific reactive oxygen species generation pathways.[9] Furthermore, SGLT2 inhibitors may reduce ectopic fat deposition and associated proinflammatory cytokine and adipokine release, influencing cardiac and vascular remodeling. Finally, ketonemia associated with SGLT2 inhibitors, specifically through β-hydroxybutyrate, could have antioxidant and anti-inflammatory effects by inhibiting histone deacetylases and NLRP3 inflammasomes.

Abbreviations and Acronyms

HFpEF	heart failure with preserved ejection fraction
IL	interleukin
LV	left ventricular
SGLT2	sodium-glucose cotransporter-2

Future Directions

Future research should focus on delineating the precise inflammatory mechanisms that contribute to HFpEF. Translational studies combining basic scientific approaches with advanced imaging and biomarker strategies may shed light on the causal relationship between inflammation and HFpEF.[10] Clinical trials targeting specific inflammatory pathways are crucial. The ongoing development and refinement of anti-inflammatory agents, such as Janus kinase inhibitors and novel IL-1β inhibitors, provide opportunities to study their effects on patients with HFpEF.[10] Finally, the HERMES trial, which evaluates the effects of ziltivekimab on IL-6 inhibition, has begun enrollment. A list of upcoming clinical trials investigating inflammation and HFpEF are shown in Table I.

In conclusion, the exploration of inflammation in HFpEF is a rapidly evolving field, poised to reshape the medical community's understanding of this complex syndrome and to unveil novel therapeutic targets.

Article Information

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TABLE I. Currently Recruiting and Upcoming Clinical Trials Evaluating Inflammation in Heart Failure With Preserved Ejection Fraction

ClinicalTrials.gov identifier	Phase[a]	Intervention	Brief summary
NCT05636176	Phase 3, not yet recruiting	Ziltivekimab vs placebo	Double-blind, placebo-controlled trial to evaluate the effects of ziltivekimab (interleukin-6 inhibitor) on morbidity and mortality in patients with heart failure, ejection fraction >40%, and high-sensitivity C-reactive protein ≥2 mg/dL
NCT05637398	Phases 1 and 2, recruiting	Colchicine vs placebo	Single-blind, placebo-controlled trial to evaluate the effects of colchicine on changes in soluble ST2 levels in patients with heart failure, ejection fraction ≥50%, and diabetes or obesity (body mass index >30)
NCT04269057	Observational	Sacubitril/valsartan	Retrospective cohort study evaluating the changes in NLRP3 inflammasome with angiotensin receptor neprilysin inhibitors (sacubitril/valsartan) in patients with heart failure and ejection fraction ≥50%
NCT05093959	Phase 2, recruiting	Metformin vs placebo	Single-blind, placebo-controlled trial to evaluate the effects of metformin on peak $\dot{V}O_2$ in patients with heart failure and ejection fraction ≥50%

$\dot{V}O_2$, oxygen consumption per unit time.

[a] Phase as of May 15, 2023.

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