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Editorial

Is Targeting Inflammation the Key to Unlocking HFpEF? : Focus on Anti-Inflammatory Therapy

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ABSTRACT

Chronic inflammation plays a crucial role in the formation of atherosclerosis and is also associated with the advancement of heart failure. Clinical and epidemiological evidence has increasingly supported the link between low-grade inflammation and heart failure with preserved ejection fraction (HFpEF). From a fundamental scientific standpoint, inflammation in HFpEF has notable detrimental impacts on the endothelium and the microvasculature of the heart. HFpEF clinical studies focusing on inflammation are a sign of hope because they show a shift toward treating the condition's cause instead of just its symptoms.

Inflammation is a critical biological process, primarily acting as the body's defense against harmful stimuli such as pathogens, damaged cells, or irritants. It operates as a protective machinery to eradicate the cause of cell injury, clear out damaged tissue, and initiate repair. Acute inflammation is a short-term and intense response, marked by increased blood flow, capillary dilatation, leukocyte infiltration, and the release of soluble mediators like cytokines and histamines. In contrast, low-grade inflammation is a chronic, systemic condition marked by a persistent, though less intense, immune response. This form of inflammation is often subtle and asymptomatic, yet it continuously produces pro-inflammatory cytokines, leading to systemic effects. Unlike the self-limiting acute inflammation, low-grade inflammation can endure for extended periods, playing a significant role in the onset and progression of various chronic diseases such as obesity and type 2 diabetes, where it contributes to insulin resistance. In cardiovascular diseases (CVD), low-grade inflammation is a key factor in the development of atherosclerosis also linked to the progression of heart failure, including heart failure with preserved ejection fraction (HFpEF).[1]

HFpEF is distinct from heart failure with reduced ejection fraction (HFrEF), where the cardiac systolic function is compromised. HFpEF is a form of heart failure where the left ventricle retains its ability to preserve its systolic function, but has impaired relaxation or filling capacity during diastole. This condition results in an inefficient supply of blood to meet the body's needs, despite a normal or near-normal ejection fraction. Patients with HFpEF commonly present with symptoms like breathlessness, fatigue, and fluid retention, similar to other forms of heart failure. However, diagnosing HFpEF presents unique challenges due to its complex pathophysiology and diverse and the presence of multiple comorbid conditions like hypertension, diabetes, and obesity. Adding to the complexity is the variability in the use of diagnostic tools and criteria across different healthcare settings. Furthermore, the lack of established, effective treatments for HFpEF complicates its management, underscoring the multifaceted nature of this syndrome within the broader context of heart failure (HF).[2]

The connection between low-grade inflammation and HFpEF has been increasingly substantiated by clinical and epidemiological evidence, helping to shape our understanding of HFpEF's pathophysiology. Clinical studies have consistently shown that patients with HFpEF have elevated levels of inflammatory markers. For example, many HFpEF patients exhibit higher levels of C-reactive protein (CRP) and increased concentrations of interleukins (such as IL-6) and tumor necrosis factor-alpha (TNF-α). IL-6 and CRP have been linked to the incident of HFpEF, indicating a direct connection between inflammation and HFpEF.[3] Moreover, conditions such as obesity, diabetes, and hypertension, which are common in HFpEF, are known to be associated with chronic systemic inflammation. The coexistence of these conditions with HFpEF suggests a potential contributory role of inflammation in the disease process. Longitudinal studies have provided evidence on the role of inflammation in the development of HFpEF. Individuals with higher baseline levels of inflammatory markers are at an increased risk of developing HFpEF.[4]

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From a basic science perspective, inflammation in HFpEF has significant adverse effects on both the endothelium, the inner lining of blood vessels, and the microvasculature of the heart. This inflammatory response leads to endothelial dysfunction, which is characterized by reduced blood vessel elasticity and impaired blood flow. Microvascular dysfunction has now emerged as a crucial factor in HFpEF, contributing to diastolic dysfunction, a hallmark of this condition. Another critical aspect of HFpEF associated with chronic inflammation is myocardial remodeling, specifically fibrosis and increased heart muscle stiffness. Inflammatory cytokines, which are prevalent in HFpEF, stimulate fibroblast activity and collagen deposition within the myocardial tissue. This process results in the stiffening of the heart muscle, severely affecting the heart's ability to relax during diastole, which plays a central role in HFpEF pathology. HFpEF often occurs alongside comorbid conditions like obesity, diabetes, and hypertension, all of which are linked to chronic low-grade inflammation. This systemic inflammation worsens HFpEF by promoting stiffness both throughout the body and within the myocardium, as well as furthering endothelial dysfunction. Moreover, nitric oxide (NO), a critical vasodilator in the cardiovascular system, is intricately tied to these processes. In HFpEF, the impaired production or availability of NO contributes to endothelial dysfunction and diastolic abnormalities. NO deficiency, often a consequence of heightened inflammatory states, exacerbates microvascular dysfunction and impairs myocardial relaxation—two key factors in HFpEF progression.[5]

So, where do we stand in the pursuit of effective treatments for HFpEF, especially in the context of inflammation? With the growing body of observational evidence and mechanistic studies highlighting the pivotal role of inflammation in HFpEF pathophysiology, there has been a surge in enthusiasm for exploring anti-inflammatory therapies in clinical trials. The question that lingers is: Are we on the cusp of a breakthrough?

Several anti-inflammatory agents have been gaining attention in the field of cardiology, and while some have undergone testing in CVD, not all have been evaluated extensively in this context. Previous study has shown that patients with rheumatoid arthritis (RA) with higher CRP levels face a greater risk of HF, while those treated with methotrexate have a lower risk, especially in cases of HFpEF.[6] Methotrexate was evaluated in a trial with ischemic cardiomyopathy patients with high hsCRP levels at the start of treatment. However, the study found no significant improvements in the 6-minute walk test, quality of life, or NYHA functional class compared to the placebo group,[7] alas, no specific trials have been conducted in HFpEF patients as of now. A trial using colchicine, an NLRP inflammasome inhibitor, in HFrEF patients reduced inflammatory markers but didn't improve exercise capacity, symptoms, or reduce HF hospitalizations or mortality.[8] The ongoing COLpEF trial (NCT04857931) is examining colchicine's efficacy in reducing inflammation and enhancing left ventricular diastolic function, as well as improving the functional status and symptoms of patients with HFpEF.

The RENEWAL trial, which investigated etanercept, a TNF-α receptor decoy, in heart failure patients, did not improve clinical outcomes. Instead, there were signs of potential harm, including an increased risk of heart failure hospitalization.[9] Similar concerns were found in the ATTACH trial.[10] Yet, similar studies involving HFpEF have not been performed. Another line of investigation has focused on anakira, an IL-1 receptor antagonist, in HFpEF patients, primarily evaluating its influence on aerobic capacity. Research conducted through the D-HART Pilot and D-HART2 trials revealed that anakinra initially improved peak VO2 and exercise time. However, these improvements did not differ significantly from the placebo group after 12 weeks.[11-12] A recent proteomics study has concentrated on inhibiting the enzyme myeloperoxidase (MPO), which is responsible for producing reactive oxygen species derived from neutrophils. This study aimed to target systemic microvascular inflammation using a novel selective MPO inhibitor. The results showed a reduction in biomarker pathways that are highly correlated with clinical outcomes in HFpEF, indicating a potential benefit of this approach.[13]

Clinical trials focusing on inflammation in HFpEF are undoubtedly a beacon of hope, representing a shift towards addressing the root cause of the condition rather than solely managing its symptoms. These endeavors hold the promise of unlocking new avenues in HFpEF treatment. While there have been limited clinical trials investigating anti-inflammatory strategies in HFpEF, it remains uncertain whether inflammation plays a unique role in HFpEF compared to HFrEF. This intriguing question fuels our curiosity and compels us to seek answers. Further research is essential to gain a comprehensive understanding of the intricate inflammatory pathways and their therapeutic potential in HFpEF. In essence, we stand at a juncture where our understanding of this complex relationship is not yet complete. However, we should appreciate and applaud the recent efforts that have paved the way for future investigations. The prospect of more effective treatments for HFpEF is on the horizon, and this exciting journey continues to inspire hope for better outcomes in patients with this challenging condition.

Conflict of Interest

There is no conflict of interest.

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