

Heart Failure with Preserved Ejection Fraction Beyond the Myocardium: Systemic Inflammation as the Central Axis of Pathophysiology

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Abstract

Heart failure (HF) with preserved ejection fraction (HFpEF) is currently the most prevalent subtype of HF, particularly among older women with multiple metabolic comorbidities. Despite recent therapeutic advances, its pathophysiology remains incompletely understood and markedly heterogeneous. In 2025, Milton Packer proposed a new conceptual framework: the adipokine hypothesis. According to this hypothesis, HFpEF is a condition primarily driven by the expansion and dysfunction of visceral adipose tissue. This remodeling of adipose tissue results in altered secretion of adipokines, which are biologically active molecules with endocrine and paracrine effects on the heart, kidneys, and vascular system. The imbalance between cardioprotective and proinflammatory adipokines promotes systemic inflammation, sodium retention, volume overload, myocardial hypertrophy, and fibrosis, ultimately leading to diastolic dysfunction and exercise intolerance, which are hallmarks of HFpEF. This article reviews the main pathophysiological foundations of this hypothesis as well as the experimental and clinical evidence and therapeutic implications, which propose a unifying paradigm for understanding and managing HFpEF.

Introduction

Heart failure (HF) with preserved ejection fraction (EF) (HFpEF) accounts for approximately half of HF cases worldwide and currently represents the most prevalent subtype of the syndrome.^{1,2} HFpEF is associated with high morbidity and mortality, particularly among older women with obesity and multiple metabolic comorbidities.²

In contrast to HF with reduced EF (HFrEF), whose pathophysiology is well established and largely explained by the neurohormonal hypothesis, HFpEF has traditionally

been considered a multifactorial syndrome. In this model, conditions such as hypertension, diabetes mellitus, obesity, aging, and systemic inflammation act relatively independently, promoting myocardial remodeling and diastolic dysfunction.²⁻⁴ However, interpreting such factors as isolated mechanisms does not satisfactorily explain the relative uniformity of clinical manifestations or the variability in therapeutic responses⁵ (Table 1).

The adipokine hypothesis has thus emerged as a potential unifying axis.⁶ According to this proposal, expansion of visceral adipose tissue (VAT) promotes its transformation into a proinflammatory endocrine organ capable of secreting mediators with direct effects on the heart, kidneys, and vascular system.^{4,6} Such alterations result in an imbalance between cardioprotective and proinflammatory adipokines, favoring systemic inflammation, sodium retention, volume overload, myocardial hypertrophy, and fibrosis, ultimately leading to the characteristic clinical phenotype of HFpEF.⁴

The adipokine hypothesis does not replace previous models but rather integrates them into a broader immunometabolic framework. HFpEF is characterized by chronic systemic inflammation sustained by several sources, including VAT, endothelial dysfunction, cellular senescence, kidney and bowel alterations, and persistent immunometabolic activation.⁷ These mechanisms converge toward microvascular rarefaction, oxidative stress, increased ventricular stiffness, and impaired lusitropic reserve, which are central elements in the pathophysiology of the syndrome.^{7,8}

The hypothesis of a central role for adiposity in HFpEF was initially supported by clinical observations showing that most patients with this syndrome present central obesity associated with systemic inflammation. Longitudinal studies, such as the UK Biobank and the Framingham Heart Study, have demonstrated that visceral adiposity, assessed by imaging methods or by the waist-to-height ratio (WtHR), is an independent predictor of HFpEF development, but not of HFrEF.⁹ Additionally, a WtHR ≥ 0.5 is present in > 95% of patients with HFpEF.¹⁰ These findings have been corroborated by recent analyses of large clinical trials, such as the PARAGON-HF,¹⁰ which have shown a direct association between central adiposity, disease severity, and prognosis in HFpEF.^{6,11}

In 2018, Milton Packer et al. described the leptin-aldosterone-neprilysin axis as one of the main mediators of the interaction between adipose tissue and the cardiovascular system. This axis helps explain classic manifestations of

Keywords

Heart Failure; Adipokines; Obesity; Inflammation; Adiponectin

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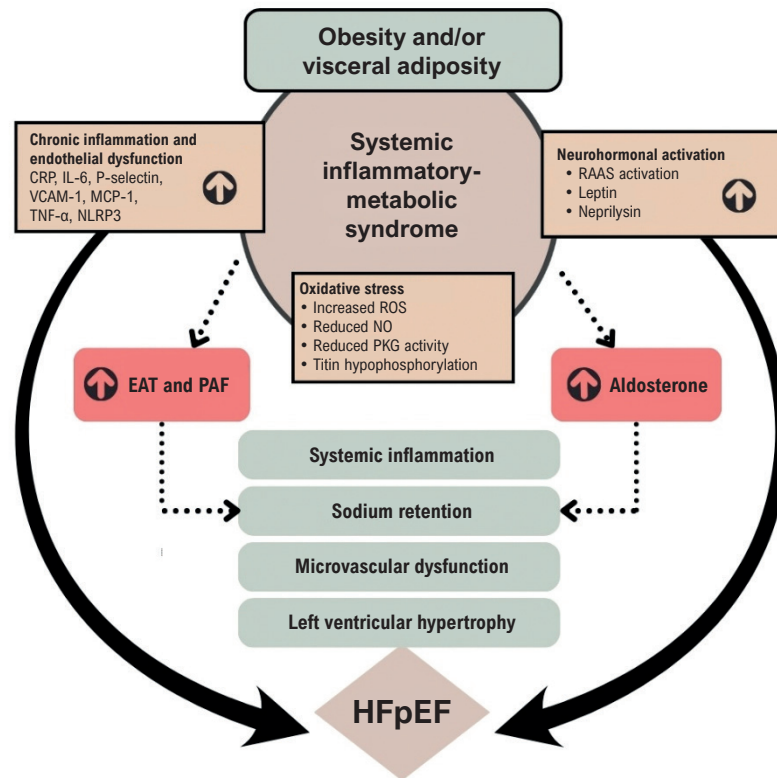
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Central Illustration: Heart Failure with Preserved Ejection Fraction Beyond the Myocardium: Systemic Inflammation as the Central Axis of Pathophysiology

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ICFEP: insuficiência cardíaca com fração de ejeção preservada; NO: óxido nítrico; ROS: espécies reativas de oxigênio; SRAA: sistema renina-angiotensina-aldosterona; TAE: tecido adiposo epicárdico; TAV: tecido adiposo visceral.

HFpEF, such as sodium retention, volume overload, and myocardial fibrosis.^{12,13}

Therefore, the aim of this article is to comprehensively review the main inflammatory pathways involved in the development and progression of HFpEF, placing the adipokine hypothesis within the broader context of the immunometabolic processes that characterize this syndrome.

Sources of systemic inflammation in heart failure with preserved ejection fraction

Visceral adipose tissue as a central inflammatory organ

Current evidence indicates that HFpEF is more strongly associated with central adiposity, often assessed by a WHtR ≥ 0.5 , than with the traditional obesity criterion based on body mass index (BMI).^{6,9-11}

VAT constitutes an important endocrine organ and, under conditions of nutritional excess, becomes metabolically active and proinflammatory. Adipocyte expansion leads to tissue hypoxia, macrophage activation,

and the secretion of adipokines with endocrine and paracrine effects. Among the systemic consequences are increased kidney and splanchnic sympathetic activity, activation of the renin-angiotensin-aldosterone system, sodium retention, volume expansion, and the development of systemic and pulmonary hypertension.^{14,15}

Concurrently, inflammatory mediators promote impairment of the coronary microcirculation and remodeling of the extracellular matrix. As a result, there is increased ventricular stiffness and decreased diastolic compliance, without significant loss of myocytes, which is a hallmark of HFpEF.^{16,17} These findings are summarized in Central Illustration.

VAT acts as an initial trigger of systemic inflammation and neurohormonal dysregulation, establishing the substrate for subsequent cardiovascular alterations.

Endothelial dysfunction, senescence, and inflammaging

Adipokines correspond to a group of bioactive molecules secreted by adipocytes, with endocrine and paracrine actions, including the subtypes described in Table 2.

Review Article

The leptin-angiotensin II-aldosterone axis is hyperactivated in central obesity. Leptin stimulates adrenal aldosterone production and may also be locally secreted by hypertrophied adipocytes through a calcineurin-dependent pathway.¹⁸⁻²¹ Sustained activation of mineralocorticoid receptors intensifies sodium retention and vascular remodeling.

Simultaneously, there is increased tubular sodium reabsorption mediated by kidney sympathetic hyperactivity. Patients with obesity exhibit decreased levels of natriuretic peptides, attributed to increased neprilysin expression and enhanced peptide clearance.^{22,23}

Within the vascular bed, leptin and aldosterone promote increased arterial stiffness and dysfunction of perivascular

Table 1 – Main hypotheses of HFpEF pathophysiology

Hypothesis	Pathophysiological mechanisms	Observational/ Experimental evidence	Proposed pretreatment	Therapeutic evidence (trials)
Hypertension-hypertrophy-diastolic dysfunction⁵	Hypertension induces myocardial hypertrophy	Hypertension is predominantly associated with HFrEF, although experimental studies suggest an association with HFpEF in early stages	Strict blood pressure control	CHARM-Preserved, PEP-CHF, and I-Preserve did not demonstrate significant mortality reduction, only modest symptomatic improvement ⁶⁵⁻⁶⁷
Microvascular inflammation associated with NO-cGMP deficiency¹⁷	Microvascular inflammation with reduced NO, cGMP, and PKG, favoring hypertrophy and interstitial fibrosis	It is not clearly established how comorbidities (diabetes, dyslipidemia, and COPD) trigger selective coronary microvascular inflammation	Drugs that increase NO or cGMP (isosorbide mononitrate, inorganic nitrite); stimulators of the cGMP pathway (vericiguat, praliquat)	NEAT-HFpEF did not demonstrate improvement in exercise tolerance with isosorbide mononitrate; meta-analyses showed no benefit with inorganic nitrite; VITALITY-HFpEF and CAPACITY-HFpEF were negative for vericiguat and praliquat ^{67,72-74}
Phenotypic mapping⁷⁵	Associated comorbidities (diabetes mellitus, hypertension, and CKD) considered determinants of distinct HFpEF subphenotypes	Phenotypic categorization into subgroups has not demonstrated consistent reproducibility	Phenotype-directed treatment (atrial phenotype: rhythm control; metabolic: SGLT2 inhibitors; vascular: antihypertensives)	EMPEROR-Preserved and DELIVER demonstrated benefit of SGLT2 inhibitors regardless of ejection fraction, suggesting an effect on the metabolic/inflammatory phenotype ^{47,48}
Adipokines⁴	Increased proinflammatory and profibrotic adipokines (leptin, resistin, TNF- α , IL-6) and reduced adiponectin, promoting systemic inflammation, endothelial dysfunction, increased cardiomyocyte stiffness, and extracellular matrix remodeling; paracrine effect of epicardial adipose tissue	Central adiposity is present in > 95% of patients with HFpEF, associated with disease development and severity	Interventions that reduce visceral adiposity and modulate adipokine production	STEP-HFpEF (semaglutide) and DELIVER/EMPEROR-Preserved (dapagliflozin, empagliflozin) demonstrated improvement in symptoms and functional capacity, reinforcing the metabolic-adipose role ⁴⁷⁻⁴⁹

CKD: chronic kidney disease; COPD: chronic obstructive pulmonary disease; HFpEF: heart failure with preserved ejection fraction; HFrEF: heart failure with reduced ejection fraction.

Table 2 – Classification and description of adipokines

Class	Subtypes/Description
Polypeptides and proteins	Adiponectin, leptin, and other proteins with endocrine and paracrine functions
Steroids and eicosanoids	Aldosterone, prostaglandins, and leukotrienes
Lipokines	Products derived from lipolysis, such as free fatty acids
Metabokines	Metabolites derived from cellular energy metabolism with signaling activity
Adipoexosomes	Extracellular nanovesicles containing proteins and microRNAs that modulate gene expression in distant tissues
Circulating mesenchymal stem cells	Cells derived from adipose tissue or bone marrow progenitors, with the ability to interact with cardiac tissue

adipose tissue.²⁴ Systemic inflammation also results in generalized endothelial dysfunction, including the coronary microcirculation.^{25,26}

Franssen et al. demonstrated that, in HFpEF, there is coronary endothelial hyperactivation, increased oxidative stress, and uncoupling of endothelial nitric oxide (NO) synthase, which begins to produce reactive oxygen species instead of NO. As a result, there is a significant reduction in NO bioavailability in the left ventricular (LV) myocardium.²⁷ The vasodilatory response to acetylcholine is decreased, contributing to diastolic dysfunction.^{16,17,27}

This process, characterized by accelerated cellular senescence, is known as inflammaging and has been associated with the pathophysiology of HFpEF.¹⁶

Cytokines and proteases amplify tissue damage, promoting hypertrophy, apoptosis, fibrosis, and abnormal myocardial repair. Endothelial inflammation is also associated with increased p53 acetylation, a pathway that plays a critical role in the transition from compensatory hypertrophy to HF. In addition, cytokine release may induce senescence in adjacent cells, establishing a feedback loop that links systemic inflammation, microvascular dysfunction, and increased ventricular stiffness, which are central mechanisms in the pathophysiology of HFpEF.^{7,28,29} (Figure 1).

Effects of inflammation on the heart

The convergence of inflammatory mechanisms results in three main alterations: endothelial dysfunction of the coronary microcirculation with capillary rarefaction, progressive interstitial fibrosis, and loss of LV lusitropic reserve.

Endothelial inflammation reduces NO bioavailability and impairs the NO-cGMP-PKG pathway, which is essential for adequate titin phosphorylation, resulting in increased cardiomyocyte stiffness.¹⁷ Decreased microvascular flow, associated with increased oxidative stress, promotes fibroblast

activation and excessive extracellular matrix deposition and culminates in diffuse fibrosis.²⁷

In parallel, impairment of the lusitropic pathway limits the diastolic capacity to accommodate increases in preload, particularly during exercise.³⁰

The leptin-aldosterone-neprilysin axis predisposes to sodium retention, volume overload, and myocardial fibrosis.^{12,13} Obesity is also associated with mitochondrial dysfunction, decreased the production of adenosine triphosphate, and intracellular calcium overload.^{31,32} Oxidation of RyR2 favors calcium leak from the sarcoplasmic reticulum, which may contribute to the occurrence of ventricular ectopy.³³

Leptin, angiotensin II, and aldosterone activate prohypertrophic and profibrotic pathways and promote increased ventricular mass.^{12,13,34} Left atrial (LA) enlargement, associated with profibrotic changes that predispose to atrial myopathy, increases the prevalence of atrial fibrillation in this population.¹⁷

Thus, obesity promotes increased volume overload through sodium retention and decreased venous capacitance, while simultaneously reducing the myocardium's adaptive capacity to this overload due to stimulation of hypertrophy and fibrosis.^{15,35} This mechanism explains the increase in filling pressures and LA volume in individuals with obesity, alterations that may be clinically relevant even in the absence of formal diagnostic criteria for HFpEF.^{24,36,37}

Experimental studies demonstrate that the development of HFpEF is associated with increased levels of specific proinflammatory adipokines in adipose tissue. Conversely, selective modulation of these adipokines may be associated with clinical improvement. In addition to preceding the development of the syndrome, alterations in levels of adipokine are also associated with greater disease severity and have prognostic value in this group of patients.⁴

The role of adipokines and Packer's hypothesis

The contemporary understanding of HFpEF has evolved to incorporate not only inflammation and microvascular dysfunction but also a profound disruption of energy-sensing pathways. Adipokines and their associated pathways thus emerge as a direct link between nutrient excess, metabolic dysfunction, and the maladaptive cardiac response.

Under conditions of nutrient scarcity, adipose tissue functions as an energy reservoir, and its capacity for regeneration and maintenance depends on mesenchymal stem cell homeostasis. Low-energy sensors, including SIRT1, AMPK, and PGC-1 α , are then activated. These pathways promote gluconeogenesis and ketogenesis, preserve mitochondrial stability, reduce oxygen consumption, and stimulate autophagy, thereby ensuring cellular renewal.³⁸

In contrast, in states of nutrient excess, expansion of VAT promotes downregulation of these pathways, resulting in oxidative stress and functional alterations of local mesenchymal cells. Consequently, adipokines are released that sustain the activation of proliferative, prohypertrophic, proinflammatory, and profibrotic pathways, both locally and systemically.³⁹

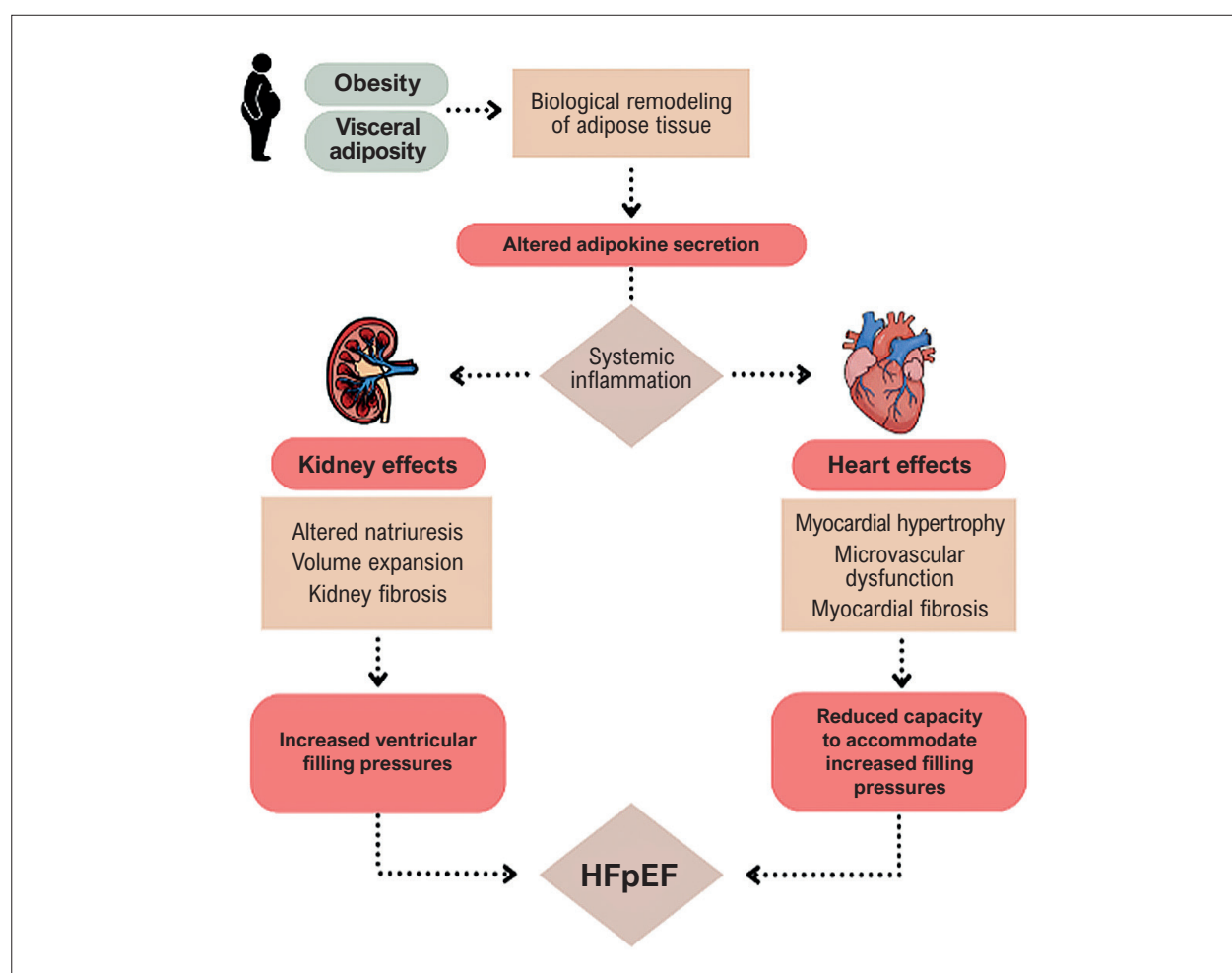


Figure 1 – Systemic and cardiorenal effects of adipokine-mediated inflammation in HFpEF. Visceral adipose tissue imbalance leads to systemic inflammation, promoting kidney effects (e.g., sodium retention and fibrosis) and cardiac effects (e.g., myocardial hypertrophy and microvascular dysfunction). These alterations result in increased ventricular filling pressures and ultimately culminate in the development of HFpEF (Adapted from Milton Packer, 2025). HFpEF: heart failure with preserved ejection fraction.

Experimental studies demonstrate that mesenchymal cells derived from adipose tissue of obese mice have the potential to induce inflammation and senescence, whereas those from healthy animals exhibit immunomodulatory and anti-inflammatory properties.⁴⁰

Another important regulator of cellular longevity is the PI3K/Akt/mTOR axis, which is essential for growth signaling and cellular proliferation.⁴¹ This axis is stimulated under conditions of nutritional excess and once activated increases mitochondrial production of reactive oxygen species, facilitating cellular proliferation. Although it is fundamental during fetal development and adaptive processes, its chronic activation in adulthood promotes cellular senescence and maladaptive hypertrophy.

Energy-sensing pathways are highly interconnected and inversely regulated. Activation of the Akt/mTOR axis, associated with suppression of SIRT1/PGC-1 α pathways modulated by adipokines released in the context of nutrient

excess, shows a remarkable parallel with the alterations observed in cardiomyocytes in HFpEF.³⁸

These metabolic alterations help explain why adipokine imbalance is not merely a marker but a central mediator of inflammation, fibrosis, and cardiac dysfunction. In this context, the model proposed by Milton Packer integrates coherently into the pathophysiological framework of HFpEF by classifying adipokines into three functional domains⁴ (Figure 2):

- Domain I:** cardioprotective, anti-inflammatory, natriuretic, and insulin-sensitizing molecules (e.g., adiponectin, omentin-1, and neuregulin-4), secreted by healthy adipocytes and suppressed in HFpEF;
- Domain II:** compensatory adipokines that increase in response to visceral adiposity (e.g., FGF21, vaspin, and IL-10), with cardioprotective effects, including inhibition of cellular stress, hypertrophy, and inflammation in white adipose tissue and the heart;

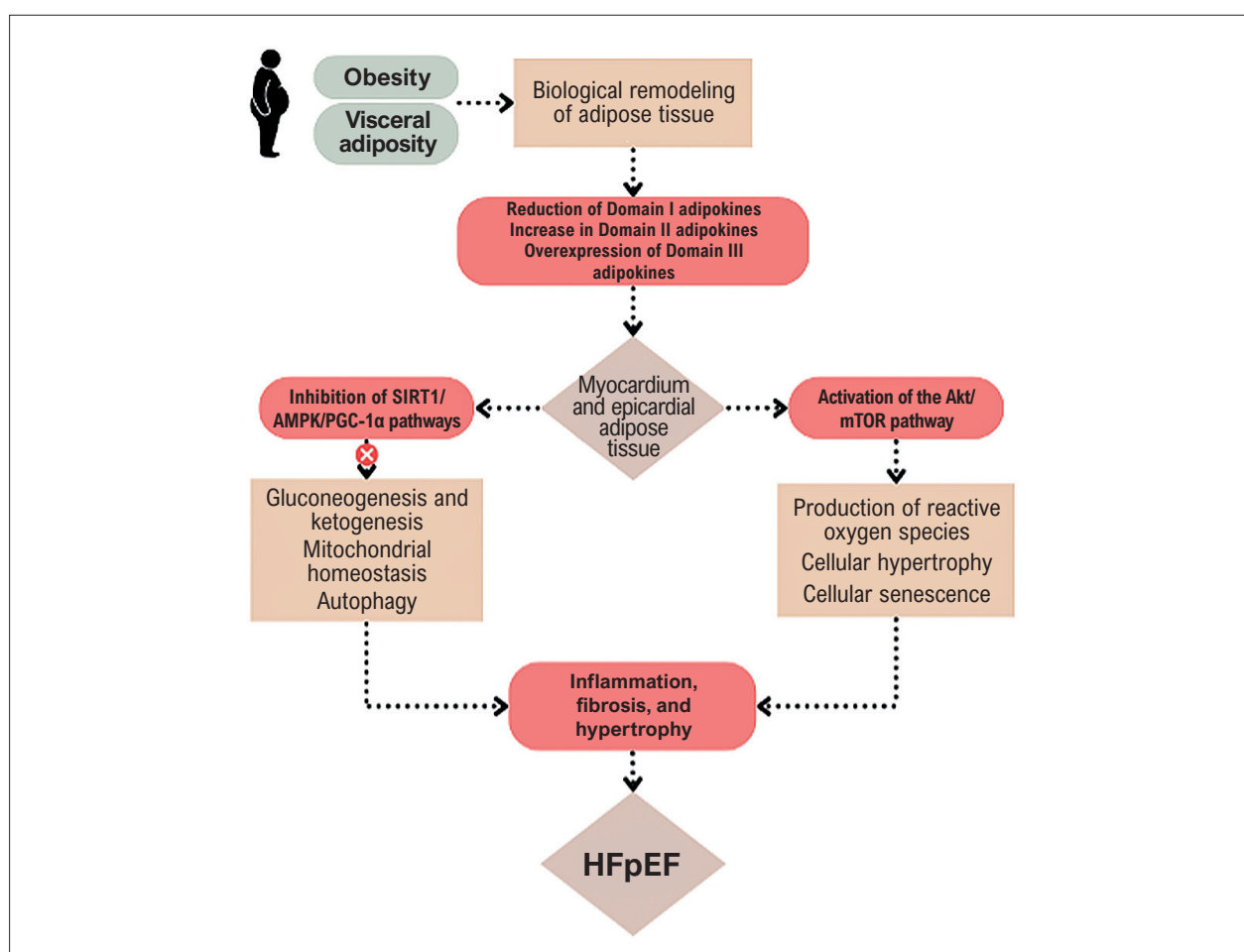


Figure 2 – Molecular mechanism of the interaction between adipose tissue and the myocardium in HFpEF. Obesity and visceral adiposity promote biological transformation of adipose tissue, resulting in an imbalance in adipokine secretion. This disruption leads to inhibition of the SIRT1/AMPK/PGC-1 α pathways and activation of the Akt/mTOR pathway. Together, these processes promote oxidative stress, inflammation, fibrosis, and myocardial hypertrophy, ultimately culminating in the clinical phenotype of HFpEF (Adapted from Milton Packer, 2025). HFpEF: heart failure with preserved ejection fraction.

3. Domain III: predominantly proinflammatory, prohypertrophic, and profibrotic adipokines (e.g., the leptin-angiotensin II-aldosterone-nephrilysin axis, autotaxin, resistin, and plasminogen activator inhibitor-1), whose expression is increased in visceral adiposity.

In visceral obesity, there is suppression of Domain I adipokines, compensatory upregulation of Domain II adipokines, and overexpression of Domain III adipokines. This imbalance establishes a proinflammatory and profibrotic hormonal environment that integrates metabolic (e.g., insulin resistance), hemodynamic (e.g., volume expansion and increased vascular resistance), and structural (e.g., myocardial hypertrophy and stiffness) alterations observed in HFpEF and its associated comorbidities. These changes may precede the clinical development of the syndrome by years, and the magnitude of adipokine imbalance correlates with disease severity and prognosis.⁴

In lean individuals, adipocytes secrete small amounts of Domain II adipokines. In visceral obesity, however, there is a marked increase in their production. Despite their cardioprotective effects, these adipokines become insufficient to prevent the development of HFpEF due to obesity-induced resistance to their biological actions. Nevertheless, patients with established HF and increased levels of these adipokines exhibit a relatively more favorable prognosis.⁴²⁻⁴⁴

Leptin is the most extensively studied of the Domain III adipokines. Under physiological conditions, it has beneficial short-term effects, such as promoting satiety, decreasing blood pressure, and protecting cardiomyocytes. However, in chronic hyperleptinemia, these effects become maladaptive, leading to the activation of the adrenergic system, increased tubular sodium reabsorption, and the induction of systemic inflammatory responses. These responses include ventricular hypertrophy, diastolic dysfunction, endothelial dysfunction, and myocardial fibrosis.¹²

The coordinated activation of the leptin-angiotensin II-aldosterone-neprilysin axis in obesity, together with the mutual amplification of its effects and signaling pathways, plays a central role in mediating the causal impact of obesity on HFpEF.⁴

Therapeutic interventions targeting the reduction of visceral adiposity, suppression of Domain III adipokines, or activation of SIRT1/AMPK/PGC-1 α pathways have demonstrated clinical and prognostic benefits in HFpEF. Among these strategies are bariatric surgery, incretin receptor agonists, SGLT2 inhibitors, mineralocorticoid receptor antagonists, and neprilysin and renin-angiotensin system inhibitors.⁴⁵⁻⁵⁰

Clinical and therapeutic evidence

Relationship between inflammatory markers and prognosis

Chronic activation of the inflammatory cascade, often originating from cardiometabolic comorbidities, promotes coronary endothelial dysfunction, increased vascular permeability, fibroblast activation, and interstitial remodeling, resulting in ventricular stiffness and diastolic dysfunction, as previously discussed.^{4,27} This process is sustained by proinflammatory cytokines and mediators derived from VAT, particularly IL-6, TNF- α , and high-sensitivity C-reactive protein (hs-CRP).^{51,52} These mediators have emerged not only as disease markers but also as prognostic determinants in HFpEF.⁴

IL-6 is a pleiotropic cytokine produced by multiple cell types, including adipocytes, macrophages, endothelial cells, and stressed cardiomyocytes.^{4,51} Its action occurs through binding to the IL-6 receptor alpha and activation of the gp130 coreceptor, triggering the JAK/STAT3 signaling pathway, in addition to modulating intracellular metabolic pathways such as mTOR and AMPK/SIRT1. From a pathophysiological perspective, IL-6 promotes TGF- β -mediated fibroblast activation, reduces titin phosphorylation, and suppresses the NO-cGMP-PKG pathway, culminating in myocardial hypertrophy, interstitial fibrosis, diastolic dysfunction, and increased oxidative stress.^{27,53}

In a multicenter study of 374 patients with HFpEF, higher levels of IL-6 were associated with higher BMI, greater prevalence of obesity, higher levels of N-terminal pro-B-type natriuretic peptide (NT-proBNP), worse kidney function, lower levels of hemoglobin, and higher levels of hs-CRP and TNF- α as well as a higher prevalence of diabetes. Such patients also exhibited lower peak VO₂ and shorter distance in the 6-minute walk test,⁵³ which suggests a direct association between decreased IL-6 and impaired functional and hemodynamic capacity.

Additional evidence is provided by a study involving 1,086 patients (506 with HFpEF and 580 with HFrEF), conducted by Berger et al.⁵² In this study, increased levels of IL-6 were significantly associated with cardiovascular mortality only in patients with HFpEF, whereas this association was not significant in HFrEF. hs-CRP showed a similar trend but did not remain significant after multivariable adjustment. There was also a significant interaction between IL-6 and NT-proBNP in predicting cardiovascular mortality. Furthermore, genotypic

analysis demonstrated that individuals homozygous for the IL6-receptor p.Asp358Ala variant (rs2228145) had significantly lower levels of NT-proBNP among patients with HFpEF, but not among those with HFrEF.⁵²

In a prospective study, patients recently hospitalized for HFpEF who had increased levels of IL-6 at discharge exhibited a higher risk of rehospitalization and mortality at 180 days.⁵⁴ In a population-based cohort of 8,534 individuals without prior HF, Chia et al. demonstrated that increased plasma IL-6 concentrations predicted the development of HFpEF but not HFrEF.⁵⁵ These findings establish IL-6 as an independent prognostic marker and a potential pathophysiological mediator in HFpEF, representing the first inflammatory biomarker with differential prognostic discrimination between HFpEF and HFrEF. Moreover, data suggest IL-6 is not only associated with disease progression but also participates in its early stages, which supports a possible causal relationship.

TNF- α in turn is a central cytokine of the inflammatory response, produced mainly by activated macrophages, T lymphocytes, and endothelial cells. It acts by promoting cardiomyocyte apoptosis, fibroblast activation, and mitochondrial dysfunction.^{56,57} In a comparative study, Putko et al. evaluated 140 patients with HF and observed that plasma levels of TNF- α and TNFR2 were significantly higher in patients with HFpEF compared with those with HFrEF, suggesting pathophysiological differences between the phenotypes.⁵⁸ Although longitudinal studies specifically focused on HFpEF remain limited, data from mixed cohorts indicate that increased levels of TNF- α are associated with increased all-cause and cardiovascular mortality, even after adjustment for NT-proBNP.⁵⁶

hs-CRP is an acute-phase protein synthesized by the liver in response to IL-6. Despite its low specificity, hs-CRP is widely used as an accessible marker of systemic inflammation and demonstrates modest but consistent prognostic value in HFpEF. In the meta-analysis by Lakhani et al., which included 19 studies and more than 4,000 patients, increased levels of hs-CRP were associated with increased cardiovascular and all-cause mortality.⁵⁹ In the study by Berger et al., hs-CRP showed lower prognostic power compared with IL-6, which suggests it reflects global systemic inflammation rather than myocardial processes specific to HFpEF.⁵² In addition, its association with prognosis appears to be influenced by metabolic status and visceral adiposity, as hs-CRP correlates with BMI and insulin resistance.^{4,60}

Most of the evidence linking IL-6, TNF- α , and hs-CRP to prognosis in HFpEF derives from observational studies, cohort analyses, and substudies of clinical trials. These designs allow identification of consistent associations but do not, in isolation, establish a direct causal relationship. Therefore, increase of such biomarkers should be interpreted as an expression of a chronic systemic inflammatory state, closely related to the cardiometabolic comorbidities that characterize HFpEF.

Definitive confirmation of the causal role of these mediators requires randomized clinical trials specifically designed for this population. In the case of IL-6, however, this limitation is partially mitigated by the convergence of multiple lines of evidence, including experimental studies demonstrating the

impact of modulation of this pathway on key processes in HFpEF pathophysiology (e.g., interstitial fibrosis, endothelial dysfunction, and increased myocardial stiffness) and genetic data associating functional variants of the IL-6 receptor with decreased levels of NT-proBNP in patients with HFpEF.

Targeted anti-inflammatory therapies

The identification of the central role of inflammation in HFpEF has, over the past two decades, driven the development of therapeutic strategies aimed at blocking proinflammatory cytokines. The evolution of these approaches reflects an important conceptual shift: from systemic and nonspecific blockade (anti-TNF) to more selective and targeted interventions (anti-IL-1 β and anti-IL-6).

TNF- α was the first therapeutic target investigated in patients with chronic HF. In the early 2000s, two major clinical trials evaluated agents blocking this pathway: etanercept (RENEWAL) and infliximab (ATTACH).^{61,62} The RENEWAL study, which integrated the RECOVER and RENAISSANCE substudies, included 2,048 patients with moderate to severe systolic HF treated with etanercept, a soluble TNF- α receptor.⁶¹ It was terminated early after interim analysis showed no benefit in mortality or hospitalization, along with a trend toward increased adverse cardiovascular events.

Similarly, the ATTACH study evaluated the monoclonal antibody infliximab in 150 patients with advanced HF.⁶² There was worsening of the composite outcomes of mortality and rehospitalization in the groups treated with higher doses, which suggests complete TNF- α blockade may negatively interfere with the physiological immune response and exacerbate endothelial and mitochondrial dysfunction.

In light of these results, the therapeutic focus shifted to the IL-1 β /IL-6 pathway. The CANTOS trial evaluated selective IL-1 β blockade with canakinumab in 10,061 patients with established atherosclerotic disease and hs-CRP ≥ 2 mg/L.^{63,64} In addition to reducing atherothrombotic events, secondary analyses demonstrated a 26% decrease in HF hospitalizations and a 17% decrease in cardiovascular mortality. These findings provided the first clinical evidence that selective modulation of inflammation can alter the course of HF. IL-1 β blockade reduces liver production of hs-CRP and consequently IL-6-mediated signaling, interrupting the proinflammatory cascade associated with myocardial remodeling and fibrosis.⁶⁴

Experimental models support these findings. In a preclinical study, pharmacological IL-6 blockade in mice subjected to subtotal nephrectomy and salt overload significantly decreased cardiac inflammatory infiltration and interstitial fibrosis, with improvement in diastolic function and reduction in oxidative stress.⁴⁵

Among IL-6-targeted therapies, the monoclonal antibody ziltivekimab stands out, as it selectively blocks this pathway. The RESCUE study demonstrated a significant reduction in levels of hs-CRP and fibrinogen in patients with chronic kidney disease (CKD) and persistent inflammation.⁶⁴ In 2024, the HERMES trial was initiated to evaluate ziltivekimab versus placebo in patients with HFpEF and systemic inflammation (hs-CRP ≥ 2 mg/L).⁴⁶ This is an ongoing study with the primary objective of assessing the impact of selective IL-6 inhibition

on hard clinical outcomes, such as cardiovascular mortality and HFpEF hospitalizations.

To date, data on clinical outcomes in patients with HFpEF treated with anti-IL-1 or anti-IL-6 therapies remain limited, as most evidence derives from secondary analyses, intermediate studies, or trials conducted in broader HF populations. Thus, the results of the HERMES study will be essential to determine whether selective cytokine inhibition translates into consistent clinical benefit in a population characterized by high clinical and pathophysiological heterogeneity.

Indirect anti-inflammatory strategies: metabolic therapies and functional immunomodulation

The adipokine hypothesis redefines the therapeutic target in HFpEF, shifting the focus from the myocardium to VAT. Strategies that modulate this tissue have demonstrated clinically relevant benefits.

Among these approaches are SGLT2 inhibitors, GLP-1 receptor agonists, selective mineralocorticoid receptor antagonists (e.g., finerenone), and interventions that promote sustained weight loss. All have shown evidence of reducing inflammatory markers, such as IL-6, TNF- α , and hs-CRP.⁴

The EMPEROR-Preserved and DELIVER trials demonstrated that empagliflozin and dapagliflozin, respectively, reduce the composite outcome of HF hospitalization and cardiovascular death in patients with HFpEF.^{65,66} Secondary analyses of these studies showed reductions in IL-6, TNF- α , and hs-CRP, suggesting a systemic anti-inflammatory effect mediated by metabolic reprogramming and immunomodulation. SGLT2 inhibition promotes increased ketogenesis and activation of AMPK/SIRT1 pathways, reducing oxidative stress and inflammatory macrophage activation.⁶⁶

GLP-1 receptor agonists have also demonstrated benefits in patients with obesity-related HFpEF. In the STEP-HFpEF study, semaglutide improved functional capacity by 20%, with a significant increase in the 6-minute walk test distance (21.5 m), in addition to marked reductions in hs-CRP (–39%) and IL-6 (–26%) after 52 weeks.⁴⁹ These effects appear to be at least in part independent of weight loss, which suggests a direct effect on systemic inflammation and improvement in microvascular function.

Finerenone, a nonsteroidal mineralocorticoid receptor antagonist, has demonstrated antifibrotic and anti-inflammatory effects in patients with HF associated with CKD. In the FIDELIO-DKD and FIGARO-DKD studies, significant reductions in inflammatory markers (IL-6, hs-CRP, and MCP-1) and major cardiovascular events were observed, reinforcing its potential as an indirect anti-inflammatory therapy in HFpEF.⁴⁹

Recent proteomic analyses have expanded the understanding of its molecular effects. In a FIGARO-DKD substudy, finerenone decreased biomarkers associated with fibrosis (e.g., osteopontin and fibronectin), inflammation, and remodeling (e.g., ANGPTL2 and CD69), in addition to suppressing neuropeptide Y, which is associated with sympathetic activation and progression of cardiac remodeling.^{67–69} Complementarily, data presented at the ESC Congress 2025, derived from proteomic analysis of the

FINEARTS-HF study, demonstrated decreased expression of profibrogenic proteins, such as CTHRC1 and CSPG4 as well as reductions in NT-proBNP and osteopontin, suggesting a direct antifibrotic and antiremodeling effect. These findings reinforce that the clinical benefits of finerenone derive not only from mineralocorticoid receptor blockade but also from integrated modulation of inflammatory pathways and the extracellular matrix, aligning with the concept of systemic inflammation and integrated remodeling in HFpEF.

Finally, reduction of VAT represents one of the main determinants of inflammatory modulation in HFpEF. Studies demonstrate that sustained weight loss, whether through dietary intervention or bariatric surgery, reduces levels of hs-CRP and IL-6, accompanied by improvement in diastolic function and myocardial stiffness. Reductions of approximately 10% in body weight may decrease serum levels of IL-6 by up to 30%, demonstrating a dose-dependent relationship between visceral adiposity and inflammation.⁶⁴

Bariatric surgery in turn decreased visceral adipose mass, increased adiponectin, and decreased leptin, PAI-1, and Gal-3, and is associated with improved functional capacity and regression of ventricular hypertrophy.^{70,71}

Conclusion

The understanding of HFpEF pathophysiology has evolved significantly in recent decades, accompanying the emergence of new paradigms in response to its high degree of conceptual and therapeutic complexity. After successive attempts to explain the condition based predominantly on hemodynamic or structural mechanisms, accumulating evidence has redirected the focus of investigation: HFpEF is not exclusively a myocardial disease but rather the cardiac manifestation of a systemic inflammatory-metabolic syndrome, in which the pathological process originates outside the heart.

The adipokine hypothesis proposed by Milton Packer represents an important conceptual milestone in understanding HFpEF. Chronic low-grade inflammation, primarily sustained by VAT dysfunction and endothelial dysfunction, provides a unifying axis capable of integrating the clinical manifestations and comorbidities associated with the syndrome. This perspective allows the interrelationship between obesity, systemic inflammation, and HF to be understood within a single pathophysiological framework.

Within this integrative model, IL-6 stands out not only as a biomarker but also as a potential active mediator of diastolic dysfunction, myocardial fibrosis, and neurohormonal activation, with direct impact on disease prognosis. Complementarily, TNF- α /TNFR and hs-CRP, although

less specific, reinforce the existence of a complex and interdependent systemic inflammatory network.

Analogous to the transformative impact of the neurohormonal hypothesis on the management of HFrEF, the adipokine hypothesis has the potential to redefine therapeutic strategies in HFpEF. However, consolidation of this new paradigm depends on evidence from randomized clinical trials specifically designed to evaluate interventions targeting visceral adiposity and associated systemic inflammation. Studies such as CANTOS and HERMES represent initial steps in this direction by investigating the clinical effects of targeted anti-inflammatory therapies.

At the same time, indirect therapies (e.g., SGLT2 inhibitors, GLP-1 receptor agonists, mineralocorticoid receptor antagonists, and interventions aimed at reducing visceral adiposity, including weight loss and bariatric surgery) demonstrate that metabolic modulation can lead to decreased systemic inflammation and functional improvement.

Taken together, these findings reinforce the notion that understanding and managing HFpEF require an integrated approach in which metabolism, inflammation, hemodynamics, and microvascular function represent interdependent components of a single systemic syndrome.

Author Contributions

Conception and design of the research, Acquisition of data, Analysis and interpretation of the data, Writing of the manuscript: Ideta MLI, Nihei CMI, Moreira PHB, Freitas AKE; Critical revision of the manuscript for intellectual content: Freitas AKE.

Potential Conflict of Interest

Ana Karyn Ehrenfried de Freitas - Participation in events/classes for Astra and Bayer.

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This article does not contain any studies with human participants or animals performed by any of the authors.

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Review Article

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