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Myocardial Chemical Modifications in Heart Failure with Preserved Ejection Fraction (HFpEF)

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Introduction

Heart Failure with preserved Ejection Fraction (HFpEF) represents a substantial and growing segment of Heart Failure (HF) cases, accounting for approximately 50% of all heart failure hospitalizations. Unlike Heart Failure with reduced Ejection Fraction (HFrEF), where the heart's ability to pump blood is diminished, HFpEF is characterized by a preserved ejection fraction (EF ≥ 50%), with primary abnormalities in diastolic function, myocardial stiffness and systemic comorbidities. This review explores the intricate myocardial chemical modifications implicated in HFpEF, emphasizing oxidative stress, inflammation, extracellular matrix remodeling and metabolic alterations.

Description

Oxidative stress and Reactive Oxygen Species (ROS)

Oxidative stress, driven by an imbalance between Reactive Oxygen Species (ROS) production and antioxidant defenses, plays a pivotal role in the pathophysiology of HFpEF. ROS, including superoxide anion, hydrogen peroxide and hydroxyl radicals, can induce cellular damage through lipid peroxidation, protein oxidation and DNA damage. In HFpEF, several sources contribute to increased ROS production:

Mitochondrial dysfunction: Mitochondria are primary sources of ROS. In HFpEF, mitochondrial biogenesis and function are often impaired, leading to excessive ROS generation. Damaged mitochondria release cytochrome c and other pro-apoptotic factors, contributing to cardiomyocyte apoptosis and fibrosis.

NADPH oxidase: This enzyme complex, particularly its isoform NOX_2, is upregulated in HFpEF. NADPH oxidase-derived ROS are involved in endothelial dysfunction and inflammation, key features of HFpEF.

Uncoupled Nitric Oxide Synthase (NOS): Under conditions of oxidative stress, NOS can become uncoupled, producing superoxide rather than Nitric Oxide (NO). This switch exacerbates oxidative stress and impairs NO signaling, crucial for vascular and myocardial function.

Inf ammation

Chronic low-grade inflammation is a hallmark of HFpEF, driven by systemic comorbidities such as obesity, hypertension, diabetes and chronic kidney disease. Inflammatory cytokines and immune cells infiltrate the myocardium, contributing to myocardial remodeling and dysfunction.

Cytokines: Elevated levels of pro-inflammatory cytokines, including tumor necrosis factor-alpha (TNF-α), Interleukin-6 (IL-6) and Interleukin-1 beta (IL-1β), are observed in HFpEF. These cytokines activate signaling pathways, such as Nuclear Factor-kappa B (NF-κB), promoting fibrosis and hypertrophy.

Macrophages: Infiltrating macrophages, particularly the pro-inflammatory M1 phenotype, secrete cytokines and ROS, exacerbating inflammation and fibrosis. Conversely, anti-inflammatory M2 macrophages, involved in tissue repair, are often diminished in HFpEF.

Endothelial cells: Endothelial dysfunction, characterized by reduced NO bioavailability and increased ROS, promotes inflammation through endothelial cell activation and adhesion molecule expression. This facilitates leukocyte adhesion and transmigration into the myocardium.

Extracellular Matrix (ECM) remodeling

ECM remodeling is a critical component of HFpEF pathophysiology, leading to increased myocardial stiffness and impaired relaxation. This process involves alterations in ECM composition, structure and turnover, mediated by various chemical modifications.

Fibrosis: Excessive deposition of collagen types I and III by activated cardiac fibroblasts results in interstitial fibrosis. Transforming Growth Factor-beta (TGF-β) is a key cytokine driving fibroblast activation and collagen synthesis. Elevated TGF-β levels correlate with worse diastolic function in HFpEF.

Matrix Metalloproteinases (MMPs) and Tissue Inhibitors of Metalloproteinases (TIMPs): MMPs are enzymes that degrade ECM components. In HFpEF, an imbalance between MMPs and TIMPs favors ECM accumulation. For example, increased MMP-2 and MMP-9 activity contributes to collagen turnover, while reduced TIMP levels fail to counteract this degradation.

Advanced Glycation End Products (AGEs): AGEs, formed through non-enzymatic glycation of proteins and lipids, accumulate in the myocardium with aging and diabetes. AGEs cross-link collagen fibers, enhancing myocardial stiffness. Additionally, AGEs interact with their receptor (RAGE), activating pro-fibrotic and pro-inflammatory pathways.

Metabolic alterations

Metabolic dysfunction is increasingly recognized as a central feature of HFpEF, impacting myocardial energy production, substrate utilization and overall cellular function.

Impaired fatty acid oxidation: The myocardium primarily relies on fatty acid oxidation for ATP production. In HFpEF, metabolic flexibility is reduced, with impaired fatty acid oxidation and a shift towards glucose utilization. This metabolic shift is inefficient, leading to energy depletion and contractile dysfunction.

Insulin resistance: Common in HFpEF patients with comorbid diabetes or obesity, insulin resistance impairs glucose uptake and metabolism. Hyperinsulinemia promotes lipid accumulation and lipotoxicity, further compromising myocardial function.

Altered AMP-Activated Protein Kinase (AMPK) signaling: AMPK is a key regulator of cellular energy homeostasis. In HFpEF, AMPK activity is often reduced, impairing mitochondrial biogenesis and function, fatty acid oxidation and glucose uptake.

Lipotoxicity: Accumulation of toxic lipid intermediates, such as ceramides and diacylglycerol, occurs in the myocardium of HFpEF patients. These lipotoxic molecules induce mitochondrial dysfunction, oxidative stress and apoptosis.

Therapeutic implications

Understanding the myocardial chemical modifications in HFpEF opens avenues for targeted therapies aimed at mitigating these pathophysiological processes.

Antioxidants: Targeting oxidative stress through antioxidants or mitochondrial protective agents holds promise. Compounds like coenzyme Q10, N-acetylcysteine and mitochondria-targeted antioxidants (e.g., MitoQ) may reduce ROS production and improve myocardial function.

Anti-inflammatory agents: Modulating inflammation through cytokine inhibitors (e.g., TNF-α inhibitors), immune cell targeting or anti-inflammatory peptides (e.g., interleukin-1 receptor antagonist) may alleviate myocardial inflammation and fibrosis.

Anti-fibrotic therapies: Agents targeting TGF-β signaling, MMP activity or AGE formation may reduce fibrosis and ECM remodeling. For instance, pirfenidone and N-acetylcysteine have shown anti-fibrotic effects in preclinical models.

Conclusion

HFpEF is a complex and multifactorial condition with diverse myocardial chemical modifications contributing to its pathophysiology. Oxidative stress, inflammation, ECM remodeling and metabolic alterations are key processes driving myocardial dysfunction in HFpEF. Advances in understanding these mechanisms offer promising therapeutic targets, aiming to alleviate the burden of this challenging condition. Future research should continue to explore these pathways, seeking novel interventions to improve outcomes for HFpEF patients.