ENDOCRINE–MICROVASCULAR COUPLING

IN THE DEVELOPMENT OF DIASTOLIC DYSFUNCTION
AND HEART FAILURE WITH PRESERVED EJECTION FRACTION

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Abstract

Heart failure with preserved ejection fraction (HFpEF) is among the most prevalent forms of heart failure in older populations and in patients with cardiometabolic and endocrine disorders. Increasing evidence supports a central role of myocardial microvascular dysfunction and endocrine–metabolic factors in the development of diastolic dysfunction, even in the absence of significant epicardial coronary artery disease.

This article provides an integrative analysis of the concept of endocrine–microvascular coupling, whereby hormonal and metabolic disturbances are viewed as key modulators of myocardial microcirculation and diastolic cardiac function. Pathophysiological mechanisms, clinical manifestations, advanced diagnostic approaches, and preventive strategies aimed at

early identification and slowing of HFpEF progression in patients with age-associated and cardiometabolic disorders are discussed.

Keywords: diastolic dysfunction, HFpEF, myocardial microcirculation, endocrine disorders, insulin resistance, endothelial dysfunction, vascular aging.

Introduction

Heart failure with preserved ejection fraction is a complex clinical and pathophysiological syndrome characterized by substantial symptoms despite relatively preserved systolic function. Unlike heart failure with reduced ejection fraction, HFpEF often develops in the setting of metabolic, endocrine, and inflammatory disturbances rather than as a consequence of isolated ischemic myocardial injury.

Accumulating data indicate that a key pathogenetic component of HFpEF is impaired left ventricular relaxation and filling, closely linked to microvascular dysfunction and endothelial impairment. Endocrine disorders—including insulin resistance, obesity, and age-associated hormonal shifts—are increasingly recognized as important modulators of these processes.

1. Diastolic Dysfunction as a Manifestation of Cardiometabolic and Endocrine Aging

Diastolic dysfunction represents a complex, multilevel phenomenon reflecting impaired active relaxation and passive filling of the left ventricle. In the context of age-associated and metabolic disorders, it does not arise as an isolated cardiac abnormality but rather as a manifestation of systemic cardiometabolic and endocrine aging, in which endocrine, inflammatory, and microvascular factors play a central role.

1.1. Metabolic Reprogramming of the Myocardium

One of the central mechanisms underlying diastolic dysfunction in HFpEF is impairment of myocardial energy metabolism. Under conditions of insulin resistance and chronic hyperinsulinemia, cardiomyocytes exhibit reduced capacity for glucose utilization, with a compensatory shift toward increased fatty acid oxidation. This metabolic alteration is associated with:

- reduced efficiency of ATP production;
- increased oxygen consumption per unit of generated energy;
- enhanced generation of reactive oxygen species;
- disturbances of calcium homeostasis, which is critical for diastolic relaxation.

Such metabolic reprogramming renders the myocardium particularly vulnerable during periods of increased demand, even in the absence of overt ischemia.

Laboratory correlates include:

- elevated fasting insulin levels;
- increased HOMA-IR index;
- moderate hypertriglyceridemia;
- reduced HDL cholesterol;
- normal or borderline fasting glucose concentrations.

Clinical–laboratory example:
A 64-year-old patient with abdominal obesity reports exertional dyspnea. Echocardiography demonstrates a left ventricular ejection fraction of 60%. Laboratory evaluation reveals HOMA-IR of 3.2, fasting insulin of 18 μIU/mL, triglycerides of 2.1 mmol/L, and HbA1c of 5.8%. These findings indicate pronounced insulin resistance in the absence of overt diabetes mellitus and help explain the energetic vulnerability of the myocardium.

1.2. Interstitial Inflammation and Myocardial Fibrosis

Chronic low-grade inflammation promotes activation of myocardial fibroblasts and remodeling of the extracellular matrix. In the presence of endocrine and metabolic disturbances, this process acquires a systemic character and leads to:

- increased interstitial fibrosis;
- reduced myocardial compliance;
- elevation of left ventricular filling pressures.

Even moderate interstitial inflammation, not accompanied by clinical or imaging signs of myocarditis, may significantly impair diastolic function.

Laboratory markers associated with this mechanism include:

- elevated high-sensitivity C-reactive protein (hs-CRP);
- increased interleukin-6 levels;
- elevated fibrinogen concentrations;
- mildly increased NT-proBNP, often within the upper reference range.

Pathophysiological example:
In a patient with HFpEF, hs-CRP is 4.1 mg/L in the absence of acute infection. Echocardiography reveals impaired left ventricular relaxation (elevated E/e’), while systolic function remains preserved. These findings support the role of systemic inflammation in the development of diastolic dysfunction.

1.3. Microvascular Hypoperfusion as a Determinant of Diastolic Vulnerability

Reduction of coronary microvascular reserve leads to relative myocardial ischemia at the cardiomyocyte level, particularly during diastole. This impairs the energetic support required for active relaxation and contributes to increased myocardial stiffness.

Indirect laboratory and functional indicators include:

- increased lactate production during exertion;
- reduced exercise tolerance;
- dissociation between clinical symptoms and absence of epicardial coronary stenoses.

Microvascular hypoperfusion thus constitutes a key link between systemic metabolic disturbances and myocardial diastolic dysfunction in HFpEF.

2. Endocrine Factors in the Pathogenesis of Diastolic Dysfunction

The endocrine system exerts a multilevel influence on cardiovascular function, including regulation of energy metabolism, vascular tone, and inflammatory activity. In the setting of age-associated disorders, endocrine alterations become important modulators of microcirculatory dysfunction and myocardial diastolic vulnerability.

2.1. Insulin Resistance and Hyperinsulinemia

Insulin resistance disrupts signaling pathways responsible for endothelium-dependent vasodilation and contributes to a reduction in coronary microcirculatory reserve. At the same time, hyperinsulinemia activates the sympathetic nervous system and pro-inflammatory cascades.

Typical laboratory profile includes:

- elevated fasting insulin levels;
- HOMA-IR > 2.5–3.0;
- normal or borderline HbA1c values;
- coexistence with dyslipidemia.

Example:
A 67-year-old woman without diabetes mellitus, HbA1c 5.7%, fasting insulin 22 μIU/mL, HOMA-IR 3.8, reports exertional dyspnea while walking. Echocardiography demonstrates grade I–II diastolic dysfunction. Classical ischemic heart disease has been excluded.

2.2. Obesity, Adipokine Imbalance, and Inflammation

Visceral adipose tissue functions as an endocrine organ secreting leptin, resistin, TNF-α, and IL-6. Concurrently, levels of adiponectin—a cardioprotective adipokine—are reduced. This adipokine imbalance enhances systemic inflammation, endothelial dysfunction, and myocardial fibrosis.

Laboratory and clinical features include:

- elevated leptin levels;
- reduced adiponectin concentrations;
- increased hs-CRP;
- increased waist circumference despite a moderate body mass index.

Example:
A patient with a body mass index of 29 kg/m² and a waist circumference of 108 cm presents with hs-CRP of 3.6 mg/L and normal glucose levels. Diastolic dysfunction is identified prior to the development of clinically overt diabetes mellitus.

2.3. Thyroid Function and Diastolic Relaxation

Even subclinical disturbances of thyroid status may affect myocardial diastolic function through regulation of calcium handling and expression of contractile proteins.

Laboratory markers include:

- moderately elevated TSH with normal free T4 levels;
- absence of overt clinical manifestations of hypothyroidism.

Example:
A 70-year-old patient with TSH of 6.2 mIU/L and normal free T4 reports fatigue. Echocardiography reveals signs of delayed myocardial relaxation.

2.4. Age-Associated Hormonal Shifts

Declining levels of estrogens, testosterone, and growth hormone are accompanied by impaired vascular reactivity, reduced microcirculatory reserve, and increased myocardial stiffness.

Clinical feature:
Diastolic dysfunction may develop even in the absence of severe conventional risk factors, underscoring the role of hormonal aging as an independent pathogenetic determinant.

3. Myocardial Microcirculation and Endocrine–Microvascular Coupling

(expanded version with laboratory and clinical evidence)

Myocardial microcirculation represents a functionally critical component of the cardiovascular system, ensuring adequate delivery of oxygen and energy substrates directly to cardiomyocytes. Unlike epicardial coronary arteries, the myocardial microvascular network determines tissue-level blood flow distribution and plays a decisive role in diastolic cardiac function.

In the context of endocrine and metabolic disorders, microcirculatory dysfunction develops as a result of complex interactions among hormonal alterations, chronic inflammatory activation, and vascular aging. This interaction constitutes the basis of the concept of **endocrine–microvascular coupling**, within which diastolic dysfunction is viewed as a consequence of impaired microvascular adaptation of the myocardium.

3.1. Functional Organization of Myocardial Microcirculation

The myocardial microcirculatory bed consists of arterioles, capillaries, and venules forming a dense and highly organized network capable of rapidly adapting to changing metabolic demands of the heart. Under physiological conditions, myocardial microcirculation is characterized by:

- high capillary density;
- pronounced capillary recruitment during stress;
- effective endothelium-dependent vasodilation;
- finely tuned autoregulation of coronary blood flow during diastole.

Diastolic myocardial perfusion is particularly sensitive to microcirculatory disturbances, as coronary blood flow occurs predominantly during the diastolic phase. Any reduction in microcirculatory reserve during this phase directly impairs myocardial relaxation.

3.2. Endocrine Mechanisms of Myocardial Microcirculatory Dysfunction

Endocrine disorders exert both direct and indirect effects on myocardial microcirculation.

3.2.1. Insulin Resistance and Coronary Microcirculatory Reserve

Under physiological conditions, insulin stimulates endothelium-dependent nitric oxide production and promotes vasodilation of coronary arterioles. In insulin resistance, this protective mechanism is impaired, while vasoconstrictive and proliferative signaling pathways remain active.

Consequences include:

- reduced coronary microcirculatory reserve;

- impaired reactive hyperemia of the myocardium;
- increased myocardial vulnerability to ischemia during exertion.

Laboratory correlates:

- elevated fasting insulin levels;
- HOMA-IR > 2.5–3.0;
- moderate hypertriglyceridemia;
- normal fasting glucose and HbA1c at early stages.

Clinical–physiological example:
A patient with insulin resistance and no epicardial coronary stenoses reports exertional dyspnea. Stress testing reveals early limitation of exercise tolerance, which is explained by reduced coronary microcirculatory reserve rather than macrovascular ischemia.

3.3. Inflammation and Microcirculatory Hypoperfusion of the Myocardium

Chronic low-grade inflammation contributes to endothelial dysfunction and impaired microvascular adaptation of the myocardium. Pro-inflammatory cytokines:

- reduce nitric oxide bioavailability;
- increase microvascular permeability;
- promote microthrombus formation;
- disrupt endothelial–pericyte interactions.

These processes result in **functional microcirculatory hypoperfusion**, particularly pronounced during tachycardia or increased myocardial demand.

Laboratory markers include:

- elevated hs-CRP;
- increased interleukin-6;
- elevated fibrinogen;
- mildly increased NT-proBNP levels.

3.4. Functional Capillary Rarefaction in the Myocardium

In contrast to advanced ischemic heart disease, HFpEF is more commonly associated with **functional**, rather than structural, reduction of capillary perfusion. A proportion of capillaries remains anatomically intact but does not participate in effective blood flow.

Mechanisms include:

- reduced capillary recruitment;
- endothelial dysfunction of arterioles;
- impaired autoregulation of coronary flow;
- microvascular spasm.

Clinical relevance:
Functional capillary rarefaction explains the frequent discrepancy between the absence of significant epicardial coronary artery disease and the presence of pronounced heart failure symptoms in patients with HFpEF.

3.5. Energetic Insufficiency and Diastolic Relaxation

Diastolic myocardial relaxation is an energy-dependent process requiring adequate ATP availability for active calcium reuptake into the sarcoplasmic reticulum. Microcirculatory hypoperfusion leads to:

- reduced energetic reserve of cardiomyocytes;
- impaired calcium homeostasis;
- delayed myocardial relaxation;
- increased left ventricular filling pressures.

Pathogenetic example:
Even transient episodes of microcirculatory hypoperfusion during physical exertion may cumulatively contribute to the progression of diastolic dysfunction in patients with HFpEF.

3.6. Arterial Stiffness and Diastolic Coronary Perfusion

Increased arterial stiffness further compromises diastolic coronary perfusion, amplifying the adverse effects of microcirculatory dysfunction. Early reflection of the pulse wave increases left ventricular afterload and shortens the duration of effective diastolic perfusion.

Together, arterial stiffness and microcirculatory dysfunction form a **vicious cycle** that exacerbates myocardial diastolic insufficiency.

3.7. Clinical and Diagnostic Implications of Endocrine–Microvascular Coupling

The concept of endocrine–microvascular coupling explains several characteristic clinical features of HFpEF:

- significant symptoms in the absence of macrovascular coronary disease;

- dissociation between preserved ejection fraction and symptom severity;
- limited effectiveness of conventional antianginal therapies.

Diagnostic indicators include:

- reduced coronary microcirculatory reserve (PET, stress CMR);
- evidence of endothelial dysfunction;
- laboratory signs of inflammation and insulin resistance.

3.8. Reversibility Potential of Myocardial Microcirculatory Disorders

At early stages, myocardial microcirculatory abnormalities retain a degree of reversibility. Correction of endocrine and metabolic disturbances may:

- improve microcirculatory reserve;
- reduce the severity of diastolic dysfunction;
- slow progression of HFpEF.

This underscores the importance of early identification of endocrine–microvascular abnormalities and implementation of comprehensive preventive strategies.

4. Clinical Manifestations and Advanced Diagnostic Assessment of HFpEF

(PET, CMR Perfusion, Invasive Microcirculatory Evaluation, and Biomarkers)

Heart failure with preserved ejection fraction is characterized by clinical manifestations of heart failure in the presence of preserved or near-preserved left ventricular ejection fraction. However, its pathogenetic substrate frequently involves myocardial microvascular dysfunction, chronic inflammation, and endocrine–metabolic disturbances. Accordingly, diagnostic assessment must extend beyond conventional evaluation of systolic function and include detailed analysis of diastolic properties, filling pressures, microcirculatory reserve, and laboratory markers of inflammation and metabolic stress.

4.1. Clinical Phenotype of HFpEF and Diagnostic Pitfalls

Typical symptoms of HFpEF include exertional dyspnea, reduced exercise tolerance, early fatigue, and episodic peripheral edema. Diagnostic interpretation is often complicated by the frequent coexistence of conditions that may obscure the cardiac origin of symptoms:

- obesity and physical deconditioning;
- arterial hypertension with increased pulse pressure;

- metabolic syndrome and insulin resistance;
- atrial fibrillation, both as a consequence and a contributor to elevated filling pressures.

Clinical example (diagnostic pitfall):
A 68-year-old patient with obesity reports progressive exertional dyspnea. Left ventricular ejection fraction is 60%, and no significant coronary stenoses are detected. Symptoms are initially attributed to excess body weight; however, advanced evaluation reveals elevated filling pressures and reduced microcirculatory reserve, consistent with HFpEF.

4.2. Echocardiography as a Foundational Tool: Diastolic Function and Filling Pressures

Echocardiography remains the cornerstone of initial HFpEF assessment, provided that attention is focused on diastolic rather than systolic parameters.

Key echocardiographic markers include:

- E/e' ratio as an indirect estimate of left ventricular filling pressure;
- early diastolic myocardial velocity (e') reflecting impaired relaxation;
- left atrial volume index as a marker of chronic pressure overload;
- tricuspid regurgitation velocity and estimated pulmonary artery pressure;
- global longitudinal strain (GLS) as an indicator of subclinical myocardial dysfunction.

Instrumental example:
A patient with preserved ejection fraction demonstrates enlarged left atrial volume and elevated E/e', indicating chronically increased filling pressures despite relatively mild symptoms at rest.

4.3. PET Myocardial Perfusion Imaging and Coronary Microvascular Flow Reserve

Positron emission tomography (PET) with quantitative assessment of myocardial blood flow represents one of the most informative techniques for diagnosing coronary microvascular dysfunction. PET enables evaluation of:

- absolute myocardial blood flow at rest and during stress;
- coronary (myocardial) flow reserve (MFR);
- regional perfusion heterogeneity in the absence of epicardial coronary artery disease.

Reduced MFR is considered a functional marker of coronary microvascular dysfunction and has been strongly associated with diastolic dysfunction and clinical manifestations of HFpEF.

Clinical example (PET):
A patient with exertional dyspnea and preserved ejection fraction undergoes PET imaging.

Coronary angiography shows no obstructive disease; however, PET reveals reduced MFR, confirming a microvascular basis for impaired myocardial perfusion and supporting the concept of endocrine–microvascular coupling.

4.4. Cardiac Magnetic Resonance Imaging with Perfusion and Tissue Characterization

Cardiac magnetic resonance imaging (CMR) provides comprehensive assessment of myocardial perfusion, structure, and tissue composition, offering unique insights into the mechanisms underlying HFpEF.

Key diagnostic capabilities of CMR include:

- stress perfusion imaging for detection of microvascular ischemia;
- T1 mapping and extracellular volume (ECV) quantification as markers of diffuse interstitial fibrosis;
- late gadolinium enhancement (LGE) for focal fibrosis;
- T2-based techniques (in research protocols) to assess myocardial edema or inflammation.

Clinical example (CMR perfusion and fibrosis):
In a patient with HFpEF, CMR demonstrates reduced stress perfusion without epicardial stenosis and moderately increased ECV, consistent with diffuse interstitial remodeling and microvascular dysfunction driven by chronic inflammation and metabolic stress.

4.5. Invasive Assessment of Coronary Microcirculation

In selected cases with diagnostic uncertainty, invasive evaluation of coronary microcirculation may be employed to distinguish epicardial from microvascular mechanisms of ischemia and diastolic dysfunction.

Key invasive parameters include:

- coronary flow reserve (CFR);
- index of microcirculatory resistance (IMR);
- endothelial function testing in specialized centers.

Invasive example:
A patient without obstructive coronary disease exhibits reduced CFR and elevated IMR, confirming microvascular dysfunction as the primary contributor to symptoms and diastolic vulnerability.

4.6. Biomarkers of HFpEF and the Microvascular–Inflammatory Phenotype

Biomarkers play an important adjunctive role in HFpEF diagnosis by supporting the clinical diagnosis and characterizing the dominant pathogenetic phenotype.

4.6.1. Natriuretic Peptides

- BNP and NT-proBNP reflect hemodynamic stress; in HFpEF, levels may be modest and influenced by obesity.

4.6.2. Inflammatory Markers

- high-sensitivity C-reactive protein (hs-CRP);
- interleukin-6 (in extended or research settings);
- fibrinogen.

4.6.3. Fibrosis and Remodeling Markers

- soluble ST2;
- galectin-3;
- markers of collagen turnover (where available).

4.6.4. Endocrine–Metabolic Profile

- fasting insulin and HOMA-IR;
- HbA1c, often in the borderline range;
- lipid profile (elevated triglycerides, reduced HDL cholesterol);
- indices of visceral obesity (waist circumference);
- thyroid function tests (TSH, free T4) when clinically indicated.

Integrated laboratory example:
A 66-year-old patient shows mildly elevated NT-proBNP, hs-CRP 3–5 mg/L, elevated fasting insulin with HOMA-IR > 3, hypertriglyceridemia, and reduced HDL cholesterol. Despite preserved ejection fraction, echocardiography reveals diastolic dysfunction, supporting a cardiometabolic and microvascular HFpEF phenotype.

4.7. Integrative Diagnostic Strategy: From Symptoms to Pathogenetic Phenotype

Given the heterogeneity of HFpEF, diagnostic evaluation should aim not only to confirm heart failure but also to identify the dominant pathogenetic mechanism:

- **microvascular–endothelial phenotype** (reduced MFR/CFR, impaired reactive hyperemia, inflammatory markers);
- **fibrotic–remodeling phenotype** (increased ECV, fibrosis biomarkers);

- **cardiometabolic phenotype** (insulin resistance, visceral obesity, dyslipidemia, low-grade inflammation).

This integrative approach enhances diagnostic precision and supports personalized preventive and therapeutic strategies.

5. Prevention and Clinical Implications

of the Endocrine–Microvascular Approach to HFpEF

Contemporary understanding of heart failure with preserved ejection fraction requires a shift in focus from the treatment of established hemodynamic abnormalities toward early identification and correction of pathogenetic mechanisms underlying diastolic dysfunction. Within the framework of endocrine–microvascular coupling, prevention of HFpEF is viewed as a comprehensive strategy aimed at reducing inflammatory activity, correcting endocrine and metabolic disturbances, and preserving myocardial microcirculatory reserve.

The clinical relevance of this approach lies in the fact that key pathogenetic processes in HFpEF often precede the development of overt heart failure and may remain subclinical for prolonged periods. This creates a window of opportunity for early intervention capable of slowing or modifying the disease trajectory.

5.1. Personalization of Prevention Based on Pathogenetic Phenotype

Advanced diagnostic evaluation of HFpEF allows identification of distinct pathogenetic phenotypes, each requiring specific preventive priorities.

5.1.1. Cardiometabolic and Insulin-Resistant Phenotype

In patients with insulin resistance, visceral obesity, and chronic low-grade inflammation, primary preventive objectives include:

- reduction of insulin resistance;
- decrease in visceral adipose tissue volume;
- correction of dyslipidemia;
- attenuation of systemic inflammatory activity.

Even moderate improvement of the metabolic profile may lead to enhanced endothelial function and increased coronary microcirculatory reserve, which has direct implications for myocardial diastolic performance.

5.1.2. Microvascular–Endothelial Phenotype

When microvascular dysfunction and reduced coronary microcirculatory reserve predominate (as demonstrated by PET, stress CMR, or invasive assessment), preventive strategies should focus on:

- restoration of endothelium-dependent vasodilation;
- reduction of inflammatory impact on the vascular wall;
- improvement of microcirculatory recruitment capacity.

In this subgroup, conventional antianginal therapies are often insufficient, underscoring the need for pathogenetically oriented prevention.

5.1.3. Fibrotic–Remodeling Phenotype

In patients with evidence of diffuse interstitial fibrosis (increased ECV on CMR, elevated fibrosis biomarkers), preventive strategies should prioritize:

- suppression of chronic inflammatory activity;
- control of factors promoting fibrogenesis;
- slowing of myocardial structural remodeling.

Early identification of this phenotype is particularly important, as structural myocardial changes are less reversible than functional microvascular abnormalities.

5.2. Non-Pharmacological Strategies as the Foundation of HFpEF Prevention

5.2.1. Reduction of Visceral Obesity and Inflammation

Decreasing visceral adipose tissue volume represents one of the most effective interventions for reducing systemic inflammation and improving microcirculatory function. Clinical observations indicate that:

- improvement in microcirculatory reserve may occur before significant weight loss is achieved;
- reduction in waist circumference correlates more closely with improved diastolic function than changes in body mass index alone.

5.2.2. Physical Activity and Microcirculatory Adaptation of the Myocardium

Regular aerobic physical activity contributes to:

- enhancement of coronary microcirculatory reserve;
- improvement of endothelium-dependent vasodilation;

- reduction of inflammatory activity;
- increased energetic efficiency of the myocardium.

In the context of HFpEF, physical activity should be regarded not only as a means of improving exercise tolerance but also as a pathogenetically relevant intervention targeting microvascular dysfunction.

5.2.3. Dietary and Behavioral Factors

Anti-inflammatory dietary patterns and lifestyle modification exert additional beneficial effects on the endocrine–metabolic milieu and vascular function. Their importance is greatest at early stages of HFpEF, when endothelial and microcirculatory alterations retain reversibility.

5.3. Pharmacological Implications Within the Endocrine–Microvascular Framework

Pharmacological prevention of HFpEF should be considered adjunctive to non-pharmacological strategies and directed toward:

- optimization of endocrine and metabolic status;
- control of arterial stiffness and vascular tone;
- reduction of chronic inflammatory activity.

Therapeutic effectiveness should be evaluated not only by traditional hemodynamic endpoints but also by its impact on microcirculatory reserve and endothelial function.

5.4. Role of Dynamic Monitoring in Preventing HFpEF Progression

Advanced diagnostic techniques and laboratory markers enable dynamic assessment of preventive strategy effectiveness. Monitoring parameters such as:

- coronary microcirculatory reserve;
- inflammatory biomarkers;
- endocrine–metabolic indices;

allows timely adjustment of preventive measures before irreversible myocardial remodeling occurs.

5.5. Clinical Implications for Endocrinology and Cardiology Practice

Integration of the endocrine–microvascular approach into clinical practice facilitates:

- earlier identification of patients at high risk for HFpEF;
- explanation of symptoms in the absence of significant macrovascular disease;
- development of personalized preventive strategies;
- reduction in the likelihood of diastolic dysfunction progression.

Thus, endocrine–microvascular coupling should be viewed not merely as a theoretical construct but as a practical clinical model capable of reshaping preventive and management strategies in HFpEF.

Conclusion

Heart failure with preserved ejection fraction represents a heterogeneous clinical and pathophysiological syndrome whose development is largely determined by interactions among endocrine, metabolic, inflammatory, and microvascular mechanisms. The present analysis demonstrates that diastolic myocardial dysfunction in HFpEF should not be regarded solely as a consequence of aging or arterial hypertension, but rather as a manifestation of systemic cardiometabolic aging.

A central pathogenetic role in HFpEF is played by myocardial microcirculatory dysfunction arising in the setting of endothelial impairment, chronic low-grade inflammation, and endocrine disturbances such as insulin resistance, visceral obesity, and age-associated hormonal shifts. Reduction of coronary microcirculatory reserve and functional capillary rarefaction lead to relative energetic insufficiency of cardiomyocytes, impaired calcium handling, and progressive diastolic myocardial stiffening despite preserved systolic function.

Advanced diagnostic approaches—including quantitative assessment of myocardial blood flow by PET, perfusion and tissue characterization by cardiac magnetic resonance imaging, and evaluation of inflammatory, fibrotic, and endocrine–metabolic biomarkers—enable identification of HFpEF at preclinical and early stages. Such strategies allow more accurate risk stratification and transition from a purely syndromic diagnosis to determination of the dominant pathogenetic phenotype.

The concept of endocrine–microvascular coupling integrates these findings into a unified model that explains the frequent discrepancy between symptom severity and absence of significant macrovascular pathology in HFpEF. Recognition of myocardial microcirculation as a central element of pathogenesis provides a new perspective on the limited efficacy of conventional hemodynamically oriented therapies.

From a practical standpoint, the proposed framework emphasizes the importance of early, personalized prevention of HFpEF. Correction of endocrine and metabolic disturbances, reduction of inflammatory activity, and preservation of myocardial microcirculatory reserve emerge as key strategies capable of slowing progression of diastolic dysfunction and reducing the risk of clinically overt heart failure.

In conclusion, endocrine–microvascular coupling should be regarded not only as a theoretical paradigm but also as a clinically meaningful approach that expands diagnostic and preventive possibilities in the management of HFpEF. Integration of this concept into endocrinology and cardiology practice opens new avenues for earlier intervention, improved prognosis, and enhanced quality of life in patients with age-associated and cardiometabolic disorders.

References

1. Paulus WJ, Tschöpe C. A novel paradigm for heart failure with preserved ejection fraction: comorbidities drive myocardial dysfunction and remodeling through coronary microvascular endothelial inflammation. *Journal of the American College of Cardiology*. 2013;62(4):263–271.
2. Borlaug BA, Paulus WJ. Heart failure with preserved ejection fraction: pathophysiology, diagnosis, and treatment. *European Heart Journal*. 2011;32(6):670–679.
3. Borlaug BA. Evaluation and management of heart failure with preserved ejection fraction. *Nature Reviews Cardiology*. 2020;17(9):559–573.
4. Shah SJ, Kitzman DW, Borlaug BA, et al. Phenotype-specific treatment of heart failure with preserved ejection fraction: a multiorgan roadmap. *Circulation*. 2016;134(1):73–90.
5. Obokata M, Reddy YNV, Borlaug BA. The role of echocardiography in heart failure with preserved ejection fraction: what do we want from imaging? *Heart Failure Clinics*. 2019;15(2):241–256.

Myocardial Microcirculation and Coronary Microvascular Dysfunction

6. Camici PG, Crea F. Coronary microvascular dysfunction. *The New England Journal of Medicine*. 2007;356(8):830–840.
7. Taqueti VR, Di Carli MF. Coronary microvascular disease pathogenic mechanisms and therapeutic options. *Journal of the American College of Cardiology*. 2018;72(21):2625–2641.
8. Murthy VL, Naya M, Taqueti VR, et al. Effects of sex on coronary microvascular dysfunction and cardiac outcomes. *Circulation*. 2014;129(24):2518–2527.
9. Taqueti VR, Solomon SD, Shah AM, et al. Coronary microvascular dysfunction and future risk of heart failure with preserved ejection fraction. *European Heart Journal*. 2018;39(10):840–849.

PET Imaging and Quantitative Myocardial Blood Flow

10. Gould KL, Johnson NP, Bateman TM, et al. Anatomic versus physiologic assessment of coronary artery disease: role of PET myocardial perfusion imaging. *Journal of the American College of Cardiology*. 2013;62(18):1639–1653.

11. Murthy VL, Lee BC, Sitek A, et al. Quantitative myocardial blood flow assessment with PET: an overview. *Journal of Nuclear Cardiology*. 2018;25(2):610–625.

12. Taqueti VR, Hachamovitch R, Murthy VL, et al. Global coronary flow reserve and adverse cardiovascular events. *Journal of the American College of Cardiology*. 2015;66(4):377–387.

Cardiac MRI, Perfusion, and Myocardial Fibrosis

13. Schelbert EB, Fonarow GC, Bonow RO, Butler J. Imaging heart failure with preserved ejection fraction: diagnostic and mechanistic insights. *JACC: Cardiovascular Imaging*. 2014;7(4):413–426.

14. Schelbert EB, Messroghli DR. State of the art: clinical applications of cardiac T1 mapping. *Radiology*. 2016;278(3):658–676.

15. Puntmann VO, Voigt T, Chen Z, et al. Native T1 mapping in differentiation of normal myocardium from diffuse disease. *JACC: Cardiovascular Imaging*. 2013;6(4):475–484.

16. Ferreira VM, Schulz-Menger J, Holmvang G, et al. Cardiovascular magnetic resonance in nonischemic myocardial inflammation. *Journal of the American College of Cardiology*. 2018;72(24):3158–3176.

Endocrine and Metabolic Mechanisms in HFpEF

17. Reaven GM. Insulin resistance and human disease. *Diabetes*. 1988;37(12):1595–1607.

18. Ferrannini E, Cushman WC. Diabetes and hypertension: the bad companions. *The Lancet*. 2012;380(9841):601–610.

19. North BJ, Sinclair DA. The intersection between aging and cardiovascular disease. *Circulation Research*. 2012;110(8):1097–1108.

20. Ungvari Z, Tarantini S, Donato AJ, Galvan V, Csiszar A. Mechanisms of vascular aging. *Circulation Research*. 2018;123(7):849–867.

Inflammation, Endothelium, and Remodeling

21. Libby P. Inflammation in atherosclerosis. *Nature*. 2002;420(6917):868–874.

22. Donato AJ, Machin DR, Lesniewski LA. Mechanisms of dysfunction in the aging vasculature and role in age-related disease. *Circulation Research*. 2018;123(7):825–848.

23. Seals DR, Jablonski KL, Donato AJ. Aging and vascular endothelial function in humans. *Clinical Science (London)*. 2011;120(9):357–375.

24. Ferrucci L, Fabbri E. Inflammageing: chronic inflammation in ageing, cardiovascular disease, and frailty. *Nature Reviews Cardiology*. 2018;15(9):505–522.

Biomarkers, Fibrosis, and Clinical Stratification

25. Januzzi JL, Prescott MF, Butler J, et al. Association of change in N-terminal pro–B-type natriuretic peptide following initiation of sacubitril/valsartan with cardiac structure and function in HFpEF. *JAMA*. 2019;322(11):1085–1095.

26. Bayes-Genis A, Zamora E, Lupón J. Galectin-3 in heart failure: linking fibrosis, remodeling, and inflammation. *Heart Failure Clinics*. 2018;14(1):73–81.

27. Santhanakrishnan R, Wang N, Larson MG, et al. Circulating biomarkers of fibrosis and risk of heart failure with preserved ejection fraction. *Journal of the American College of Cardiology*. 2017;70(24):2986–2997.