Reviews in Cardiovascular Medicine

Rev. Cardiovasc. Med. **2026**; 27(11): 51621
https://doi.org/10.31083/RCM51621

Review

Re-Examining and Improving the Role of Natriuretic Peptides in the Clinical Dilemma of HFpEF Management

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Academic Editor: Alessandro Cataliotti

Submitted: 8 March 2026 Revised: 10 June 2026 Accepted: 16 June 2026 Published: 10 November 2026

Abstract

Heart failure with preserved ejection fraction (HFpEF) accounts for a large and growing proportion of heart failure, yet its diagnosis and treatment remain challenging because guideline-defined HFpEF encompasses several clinical phenotypes. Natriuretic peptide (NP) concentrations in HFpEF are often lower, or only mildly elevated, compared with those in heart failure with reduced ejection fraction (HFrEF). These values may reflect obesity, rhythm status, renal function, measurement timing, or the absence of overt congestion, as well as true impairment of NP synthesis, processing, clearance, or downstream signaling. This review synthesizes clinical and experimental evidence on NP heterogeneity in HFpEF, reassesses the limitations of fixed diagnostic thresholds, and discusses multi-marker strategies for contextual interpretation. We present functional NP deficiency as a hypothesis-generating framework, rather than a stand-alone diagnostic entity, to help organize future studies of NP axis biology, phenotypic stratification, and precision management in HFpEF.

Keywords: heart failure; natriuretic peptides; biomarkers; signal transduction; diastolic ventricular function; precision medicine

1. Introduction

Heart failure with preserved ejection fraction (HFpEF) now accounts for more than half of heart failure cases worldwide, imposing an increasing burden on health-care systems [1,2]. Unlike heart failure with reduced ejection fraction (HFrEF), which benefits from established disease-modifying therapies, HFpEF remains a clinically heterogeneous syndrome with limited treatment options and suboptimal outcomes [3]. B-type natriuretic peptide (BNP) and N-terminal pro-B-type natriuretic peptide (NT-proBNP) are established biomarkers for heart failure diagnosis and management [4,5,6]. In HFpEF, however, natriuretic peptide (NP) values may be lower or only mildly elevated despite symptoms, structural abnormalities, or elevated filling pressures, creating uncertainty about how NP measurements should be interpreted in this population [7].

Recent evidence suggests that a subset of patients with well-characterized HFpEF may have relative impairment of the NP axis, involving reduced cardiac synthesis, accelerated peripheral clearance, defective peptide processing, or attenuated downstream cyclic guanosine monophosphate (cGMP) signaling [8,9,10]. Importantly, low NP values do not by themselves prove intrinsic NP axis dysfunction; they should first be interpreted in relation to diagnostic certainty, congestion status, body composition, atrial rhythm, renal function, and the clinical setting.

This review synthesizes current clinical and experimental evidence to re-evaluate the role of NPs in HFpEF, discusses the limitations of current diagnostic thresholds, and examines phenotype-specific therapeutic strategies within a precision-based management framework.

2. Literature Search Methodology

This narrative review used a structured literature search rather than a formal systematic-review protocol. PubMed/MEDLINE, and Web of Science were searched and updated for publications from January 2000 to June 2026, supplemented by manual screening of reference lists from key articles. The following Medical Subject Headings (MeSH) terms and keywords were used: “Heart Failure”, “Heart Failure, Diastolic”, “Natriuretic Peptides”, “Biomarkers”, “Signal Transduction”, “Ventricular Function, Diastolic”, “Precision Medicine”, “HFpEF”, “BNP”, “NT-proBNP”, “atrial natriuretic peptide (ANP)”, “natriuretic peptide receptor”, “natriuretic peptide receptor-C (NPR-C)”, “cGMP-protein kinase G (PKG) signaling”, “neprilysin”, “sacubitril/valsartan”, “sodium-glucose cotransporter-2 (SGLT2) inhibitors”, and “glucagon-like peptide-1 (GLP-1) receptor agonists”. Original research articles, systematic reviews, meta-analyses, and authoritative clinical guidelines were included when they addressed NP biology, HFpEF pathophysiology, diagnosis, or treatment. Case reports, conference abstracts without full text, and studies focused exclusively on HFrEF without relevant comparison to HFpEF were excluded. Evidence was qual-

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Table 1. Key factors and mechanisms of NP system dysregulation in HFpEF.

Factor	Effect on NP axis	Primary mechanism	References
Atrial fibrillation	↑Increased	Increased atrial wall stretch and remodeling.	[7,15,17]
Renal impairment	↑Increased	Reduced renal clearance of peptides.	[16]
Obesity	↓Decreased	Altered NPR-C expression in adipose tissue, potentially contributing to enhanced NP clearance.	[14,24]
Metabolic syndrome	↓Decreased	Stress-transcription coupling failure.	[22,23]
Potential Alterations in NP Processing	Possible reduction in bioactive BNP availability	Altered proBNP glycosylation and/or corin/furin-mediated cleavage may affect mature BNP generation; HFpEF-specific processing impairment remains unconfirmed.	[18,19,20]
Oxidative stress	↓Signaling	cGMP-PKG pathway impairment.	[21]

↑ = increased, ↓ = decreased. NP, natriuretic peptide; HFpEF, heart failure with preserved ejection fraction; NPR-C, natriuretic peptide receptor-C; proBNP, pro-B-type natriuretic peptide; cGMP, cyclic guanosine monophosphate; PKG, protein kinase G; BNP, B-type natriuretic peptide.

itatively appraised according to study design and clinical relevance, with greater weight given to randomized trials, prospective cohorts, guideline statements, and mechanistic studies with direct relevance to NP axis biology.

3. Clinical Heterogeneity of Natriuretic Peptide Levels in HFpEF

Circulating NP levels in HFpEF exhibit marked heterogeneity and are often substantially lower than those observed in HFrEF. This variation is influenced by patient phenotype, comorbidities, renal function, atrial rhythm, and the timing of measurement relative to congestion or decongestion. Therefore, NP concentrations should be interpreted as context-dependent signals rather than as isolated markers of disease presence or severity.

In patients with HFpEF characterized by obesity and metabolic syndrome, NP levels are often low. Approximately 13.7% of hospitalized patients labelled as HFpEF exhibit low NT-proBNP levels (<300 ng/L) despite meeting diagnostic criteria. These patients tended to have higher body mass index (BMI) and a lower incidence of atrial fibrillation, indicating that NP levels do not always accurately reflect hemodynamic severity or clinical risk [11]. Nevertheless, such observations should not be interpreted automatically as primary NP axis failure. Low NP concentrations should also prompt reassessment of diagnostic certainty, objective congestion, and alternative causes of dyspnea. While NPs retain prognostic value for mortality and cardiovascular events in this population, their sensitivity and risk-stratification capacity are diminished by high BMI [12]. This reduction may be associated with altered NPR-C expression in adipose tissue and metabolic factors such as insulin resistance [13,14].

Conversely, atrial fibrillation (AF) and renal impairment act as potent stimuli for NP elevation. AF markedly increases BNP/NT-proBNP levels beyond those seen in sinus rhythm due to atrial remodeling and stretch, necessitating rhythm-adjusted diagnostic thresholds [7,15]. Similarly, both BNP and NT-proBNP levels rise as the estimated glomerular filtration rate (eGFR) declines, particularly below 60 mL/min/1.73 m^2, due to reduced renal clearance and the synergistic pathophysiology of cardiorenal syndrome [16]. In summary, while high NP levels remain strongly correlated with adverse outcomes in HFpEF, the considerable heterogeneity across phenotypes suggests that absolute quantitative thresholds are insufficient [12]. Effective clinical interpretation requires a holistic approach that integrates rhythm status, body composition, and renal function.

4. Multilevel Pathogenic Mechanisms of NP System Dysfunction in HFpEF

In HFpEF, NP system abnormalities should be interpreted as part of broader systemic remodeling across synthesis, processing, clearance, and signaling. In selected phenotypes, this remodeling may produce a relative functional NP deficiency, in which circulating concentrations are lower than expected for the degree of objectively demonstrated hemodynamic stress. The key factors and mechanisms of NP system dysregulation in HFpEF are summarized in Table 1 (Ref. [7,14,15,16,17,18,19,20,21,22,23,24]).

4.1 Impaired Myocardial Synthesis and Secretion: The Starting Point for Insufficient Natriuretic Peptide Production

In well-phenotyped HFpEF cohorts, elevated diastolic filling pressure and increased myocardial stiffness are frequently observed, but these features are not universal across unselected populations. Unlike the eccentric remodeling in HFrEF, the mechanical strain pattern in HFpEF may attenuate the transcriptional response of the natriuretic peptide B (*NPPB*) gene. HFpEF often coexists with obesity, insulin resistance, and chronic low-grade inflammation. These metabolic-inflammatory states can suppress mechanical stress-induced BNP transcription through pathways such as phosphoinositide 3-kinase (PI3K)-protein kinase B (Akt), nuclear factor κB (NF-κB), and mitogen-activated protein kinase (MAPK) signaling cascades. Evidence suggests that in obesity-related HFpEF, myocardial *NPPB* messenger ribonucleic acid (mRNA) expression may

fail to increase proportionally despite elevated left ventricular filling pressures, indicating a potential uncoupling between hemodynamic stress and transcriptional NP response [22,25,26]. Mechanistic studies have identified specific inflammatory signaling pathways that mediate this suppression. A review by Clerico et al. [23] summarized that the obesity-related reduction in BNP levels may involve multiple mechanisms, including enhanced clearance by adipose tissue and possible downregulation of *NPPB* transcription via PI3K-Akt signaling related to insulin resistance. These earlier mechanistic studies complement the more recent clinical observations from Ostrominski et al. [27].

4.2 Increased Peripheral Clearance

Enhanced peripheral clearance significantly contributes to the low NP levels observed in HFpEF. NPR-C, highly expressed in adipose tissue, mediates the endocytosis and degradation of NPs. Obese individuals have lower circulating natriuretic peptide levels than non-obese individuals, and this association persists after adjustment for clinical and echocardiographic measures of cardiac structure [28,29]. Obesity is associated with insulin resistance, chronic low-grade inflammation, and reduced circulating natriuretic peptide levels. Altered natriuretic peptide handling in adipose tissue, including enhanced NPR-C-mediated clearance, has been proposed as a potential contributor to this natriuretic peptide deficiency [23,24,30].

Although obesity increases the risk for development of heart failure (HF), it is associated with a protective effect on clinical outcomes in established HF. Compared to individuals with normal or low BMI, overweight and obese patients have the advantage of higher survival rates and lower mortality rates, a phenomenon termed the obesity paradox [31,32]. However, in HFpEF, obesity is increasingly recognized as a key pathophysiological driver rather than merely a protective phenotype present in a large proportion of patients with established HFpEF [25]. Therefore, the interpretation of the ‘obesity paradox’ in HFpEF requires caution.

Available evidence indicates that weight loss can modulate the NP system. In one study, weight loss was associated with reduced natriuretic peptide receptor 3 gene (*NPR3*) mRNA expression in adipose tissue and increased expression of the natriuretic peptide signaling receptor NPR-A, suggesting a potential improvement in NP bioavailability [33]. In a cohort of 12 patients with morbid obesity (BMI >35 kg/m^2), standardized intravenous BNP infusion before and after bariatric surgery showed an approximately 30% reduction in plasma clearance of exogenous BNP after surgery. Although endogenous NP concentrations were not significantly altered, the ratio of NT-proBNP to 24-hour urinary sodium excretion increased after surgery [34]. These findings indirectly support the possibility that obesity-related HFpEF may involve altered NP clearance and signaling. In Semaglutide Treatment Evaluation in People with Obesity and HFpEF (STEP-HFpEF), semaglutide produced substantial weight loss and improved clinical status in obese HFpEF phenotypes, while changes in NT-proBNP should be interpreted within the broader context of weight loss, inflammation, and hemodynamic unloading [35].

4.3 Abnormal Processing of Natriuretic Peptides: ProBNP Accumulation With Decreased Biologic Effect

Cardiomyocytes primarily secrete the precursor proBNP, which requires cleavage by corin and furin to generate bioactive BNP. Previous studies in severe heart failure populations and experimental models have demonstrated that circulating immunoreactive BNP concentrations do not necessarily reflect the availability of mature, biologically active BNP. However, whether comparable abnormalities in proBNP processing occur in patients with HFpEF remains uncertain. A landmark study by Hawkridge et al. [18] used quantitative mass spectrometry in patients with severe heart failure (phenotype not specified) and found that despite extremely high BNP immunoreactivity measured by point-of-care testing (>290 fmol/mL), no endogenous mature 32-amino-acid BNP (BNP-32) was detectable in any of the heart failure samples. This finding demonstrated that circulating “BNP” detected by conventional immunoassays does not necessarily represent the mature, biologically active BNP-32, and suggested that incompletely processed proBNP or other molecular forms predominate in severe heart failure. While not specific to HFpEF, this observation suggests that caution is needed when interpreting NP immunoassay results across heart failure phenotypes, and similar mechanisms may also operate in selected HFpEF populations [18].

Subsequent *in vitro* studies have identified a potential molecular mechanism for this phenomenon. Using cell expression systems and site-directed mutagenesis, Semenov et al. [19] showed that O-glycosylation of proBNP at threonine residue 71 specifically blocks its proteolytic cleavage by furin *in vitro*, suggesting that glycosylated proBNP is a poor substrate for processing into mature BNP and NT-proBNP. Tonne et al. [36] proposed a revised model in which normal cardiomyocytes secrete glycosylated proBNP1-108 as the predominant form. This challenges the earlier paradigm that only diseased hearts secrete unprocessed proBNP. Their findings also raise the possibility that altered glycosylation patterns in disease states could influence proBNP processing efficiency, although the direction and functional significance of such changes require further investigation [36].

In a study of 309 patients with acute dyspnea (including 142 with confirmed heart failure, HF phenotype not specified), Røsjø et al. [37] found that deglycosylation increased measured NT-proBNP concentrations from a median of 3588 ng/L to 7497 ng/L in HF patients, improved diagnostic area under the receiver operating characteristic

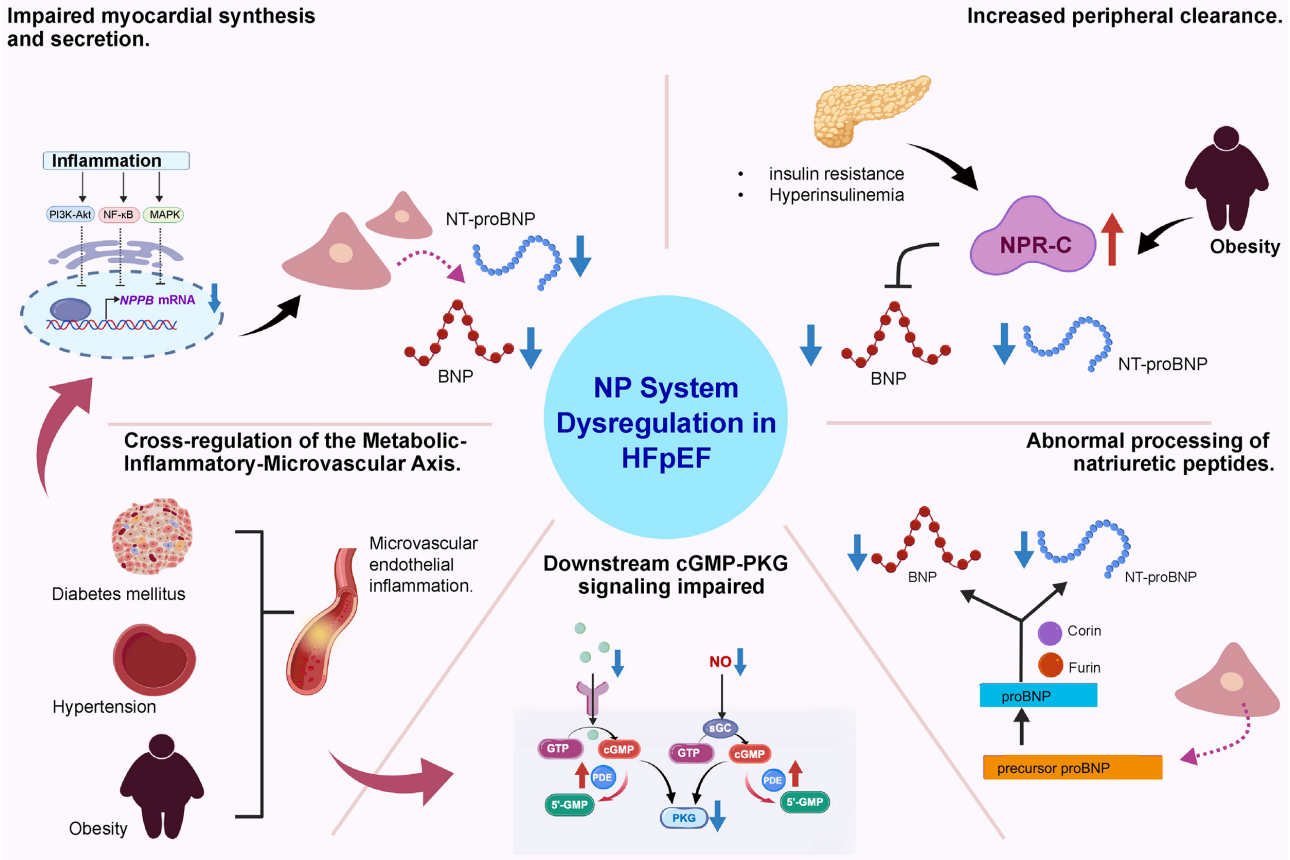


Fig. 1. Pathophysiological framework of the natriuretic peptide (NP) axis and functional deficiency in HFpEF. PI3K, Phosphoinositide 3-kinase; Akt, Protein kinase B; NF-κB, nuclear factor kappa B; MAPK, mitogen-activated protein kinase; GTP, guanosine triphosphate; GMP, guanosine monophosphate; NO, nitric oxide; sGC, soluble guanylate cyclase; PKG, protein kinase G; PDE, phosphodiesterase; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NPR-C, natriuretic peptide receptor-C; HFpEF, heart failure with preserved ejection fraction; cGMP, cyclic guanosine monophosphate; *NPPB*, natriuretic peptide B; mRNA, messenger ribonucleic acid.

curve (AUC) from 0.852 to 0.871, and yielded a net reclassification improvement of 0.24 for all-cause mortality. These findings demonstrate that proBNP glycosylation status affects NT-proBNP measurement accuracy. However, whether this phenomenon specifically accounts for the NP profiles observed in HFpEF requires dedicated investigation in well-phenotyped HFpEF cohorts.

Corin and furin participate in natriuretic peptide precursor processing through distinct proteolytic mechanisms. Corin is a type II transmembrane serine protease synthesized as an inactive zymogen and activated primarily by proprotein convertase subtilisin/kexin type 6 (PCSK6) at the cardiomyocyte surface [38]. Activated corin cleaves proANP to generate biologically active ANP and may also contribute to proBNP processing. In contrast, furin can directly cleave proBNP to generate biologically active BNP and NT-proBNP, without acting as the principal activator of corin [39]. Collectively, these findings support the biological plausibility of altered proBNP processing as a potential mechanism contributing to discrepancies between immunoreactive NP concentrations and bioactive peptide availability. However, most of the available evidence originates from severe heart failure populations, systolic heart failure, or experimental studies. Therefore, whether similar processing abnormalities occur in HFpEF, and to what extent they contribute to the heterogeneous NP profiles observed in this population, remains to be established. Direct investigations of proBNP molecular forms, glycosylation patterns, and corin/furin activity in well-characterized HFpEF cohorts are needed to clarify this potential mechanism.

4.4 Impaired Downstream cGMP-PKG Signaling

Even when circulating NP concentrations are measurable, their biological effects require cGMP generation and activation of PKG through NPR-A signaling. In HFpEF, cGMP-PKG signaling may be impaired by reduced NPR-A expression or function, enhanced phosphodiesterase activity, oxidative stress, and reduced nitric oxide (NO)-soluble guanylate cyclase (sGC) signaling [9].

The potential role of reduced PKG activity in myocardial stiffness has been examined in a rat metabolic risk model of HFpEF. Hamdani et al. [40] found that titin stiffening in this model was associated with altered titin isoform composition and reduced phosphorylation at certain PKG-

dependent sites, both of which may contribute to increased left ventricular stiffness and impaired diastolic relaxation. This finding provides a mechanistic link between upstream cGMP deficiency and the hallmark diastolic dysfunction of HFpEF. Reduced PKG activity can also contribute to insufficient myocardial myosin phosphorylation and worsening diastolic dysfunction.

4.5 Cross-Regulation of the Metabolic-Inflammatory-Microvascular Axis

HFpEF is a systemic disorder where comorbidities (diabetes, hypertension, obesity) drive microvascular endothelial inflammation. This systemic state reduces nitric oxide bioavailability and suppresses cGMP production, indirectly neutralizing NP signaling. Simultaneously, chronic inflammation inhibits *NPPB* expression and promotes myocardial fibrosis, integrating the NP system into a broader dysregulated cardio-metabolic network [21,41,42] (Fig. 1).

It is important to contextualize NP axis dysfunction within the broader landscape of HFpEF pathophysiology, which is now understood through multiple complementary paradigms. The systemic inflammation paradigm, as articulated by Paulus and Tschöpe [21], posits that comorbidity-driven coronary microvascular endothelial inflammation is the central upstream driver, leading to reduced NO-cGMP-PKG signaling in adjacent cardiomyocytes—a pathway that directly intersects with NP axis dysfunction. The microvascular dysfunction paradigm highlights that impaired coronary microvascular reserve and rarefaction independently impair myocardial energetics and diastolic relaxation, creating a pathophysiological substrate that amplifies the consequences of NP deficiency [41]. Finally, the adipokine hypothesis proposes that visceral adiposity drives cardiac dysfunction through ectopic lipid deposition, adipokine dysregulation, and systemic inflammation, all of which suppress NP synthesis and accelerate clearance through *NPR-C* upregulation in adipose tissue [43]. Recognizing these intersecting paradigms underscores that NP axis dysfunction in HFpEF is not an isolated phenomenon but a convergent downstream manifestation of multiple upstream pathological processes. This multi-paradigm perspective is essential for understanding why single-target NP-centric therapies have yielded limited success and why combination approaches targeting multiple axes simultaneously represent the most promising therapeutic strategy.

5. Re-Assessment of Natriuretic Peptide as a Biomarker

While NPs are established tools for heart failure management, current diagnostic thresholds were largely derived from populations in which overt congestion and wall stress were prominent. Their accuracy in HFpEF is challenged by the fact that some patients with structural cardiac abnormalities or invasive evidence of elevated filling pressures have NP values in the normal or mildly elevated range. Conversely, low NP concentrations below commonly used rule-out thresholds, especially in acute settings, should prompt careful reconsideration of whether active congestive heart failure is present. Thus, NP abnormalities in HFpEF should be interpreted as a diagnostic and biological signal, not as definitive evidence of NP axis dysfunction in isolation.

5.1 The Limitations of Traditional Cutoff Values for HFpEF

Current BNP and NT-proBNP thresholds emphasize volume overload and wall tension, which are prominent in many HFrEF presentations. In HFpEF, diastolic dysfunction, microvascular impairment, obesity, atrial fibrillation, renal function, and treatment status can all modify the relationship between myocardial stress and circulating NP concentrations [10,16,17,23]. Consistent with this phenotypic variability, NT-proBNP concentrations may remain below conventional diagnostic thresholds in a subset of patients with objectively confirmed HFpEF. In a cohort of 420 patients with HFpEF confirmed by invasive hemodynamic assessment at rest or during exercise, Verbrugge et al. [44] reported that 157 patients (37.4%) had NT-proBNP concentrations below 125 ng/L despite elevated cardiac filling pressures. However, this proportion reflects the characteristics of a selected referral cohort and should not be generalized to the broader HFpEF population. In clinical practice, this observation should be interpreted cautiously: low NP levels may also reflect absence of overt congestion, measurement after decongestion, or inclusion of HFpEF mimics.

Clinical interpretation of NP values must account for obesity, atrial fibrillation, renal function, treatment exposure, and timing of sampling. Obesity may lower NP concentrations through increased adipose-tissue clearance and suppression of synthesis, whereas atrial fibrillation and renal impairment tend to increase BNP/NT-proBNP levels [16,17,34]. Acute decompensated HFpEF, chronic stable HFpEF, exercise-induced elevation in filling pressures, and non-cardiac dyspnea syndromes are therefore expected to show different NP profiles. A single fixed threshold may introduce systematic bias in diagnosis, trial enrolment, and mechanistic interpretation.

5.2 Diagnostic Boundaries and HFpEF Mimics

A central limitation in applying NP-based frameworks to HFpEF is diagnostic heterogeneity. Patients labelled as HFpEF may include acute decompensated HFpEF with objective congestion, chronic stable HFpEF, exercise-induced elevation in filling pressures, pulmonary or valvular disease, cardiomyopathies, renal disease, obesity-related dyspnea, and other HFpEF mimics.

The extent of this diagnostic heterogeneity has been highlighted by recent work. Bellicini [45] retrospectively analyzed 773 patients hospitalized for acute heart failure. Among 323 patients with left ventricular ejection fraction

Table 2. Integrated biomarker strategies for HFpEF phenotyping.

Combination	Clinical value/target	References
NP + GDF-15	Prognosis & metabolic stress	[47]
NP + sST2	Prognosis & myocardial stress	[48]
NP + hs-cTnT	Persistent myocardial micro-injury	[49]
NP + IL-6	Systemic inflammation-driven phenotype	[50]
NP + Metabolic Markers	Insulin resistance & adiposity-driven HFpEF	[51]
proBNP/BNP	Established diagnostic and prognostic biomarkers, with context-dependent interpretation in HFpEF	[7,10,12,52,53]

GDF-15, Growth Differentiation Factor 15; sST2, soluble suppression of tumorigenicity 2; hs-cTnT, high-sensitivity cardiac troponin T; IL-6, interleukin-6.

(LVEF) >40%, 252 (78%) showed systemic venous congestion. Of these 252 patients, 206 (81.7%) had severe valvular disease, 26 (10.3%) had other structural or rhythm disorders or stage V renal failure, and only 20 (8%) had no clear HFpEF mimic after rigorous exclusion. These findings suggest that when guideline definitions are strictly applied, HFpEF or heart failure with mildly reduced ejection fraction (HFmrEF) as an independent cause of acute decompensation may be uncommon or even rare. The clinical implication for NP interpretation is that when a patient labeled as HFpEF presents with low NP levels, the first consideration should be whether an alternative cardiac pathology (e.g., severe valve disease) or diagnostic misclassification exists, rather than automatically attributing the low NP to intrinsic NP axis dysfunction.

The diagnostic picture becomes even more complex in non-acute settings. Landsteiner et al. [46] provided a comprehensive review of exercise intolerance in HFpEF, emphasizing that many patients who meet guideline criteria for HFpEF primarily present with exertional dyspnea rather than overt volume overload at rest. Their analysis shows that exercise intolerance in these patients arises from multiple mechanisms beyond diastolic dysfunction, including left atrial pathology, right ventricular dysfunction, valvular disease, and extracardiac factors.

Landsteiner et al. [46] propose a 'domain-based phenotyping' approach that decomposes exercise limitation into quantifiable deficits in distinct physiological domains—such as chronotropic incompetence, ventricular-vascular uncoupling, and left atrial reservoir dysfunction—each of which can be measured independently and may require different therapeutic interventions. Critically, in patients whose predominant manifestation is exercise intolerance without resting congestion, left ventricular wall stress may not be substantially elevated at rest, and therefore NP levels lack a strong stimulus for elevation. Under such circumstances, low or mildly elevated NP levels may simply reflect the absence of significant resting wall stress rather than any abnormality in NP synthesis, processing, or signaling.

Taken together, these observations provide a structured framework for interpreting low or mildly elevated NP levels in patients who carry a diagnosis of HFpEF. Such values may reflect: (i) the presence of an alternative structural heart disease that mimics HFpEF, as suggested by Bellicini [45]; (ii) a clinical picture dominated by exercise intolerance without resting congestion, where NP levels are not expected to rise, as discussed by Landsteiner et al. [46]; (iii) confounding effects of obesity, atrial fibrillation, or renal impairment; or (iv) genuine functional impairment of the NP axis at the level of synthesis, processing, clearance, or signaling. Therefore, low or mildly elevated NT-proBNP should not be interpreted as a paradox by default. In patients with values below accepted rule-out thresholds, particularly during acute evaluation, the first clinical step should be reassessment of congestion and diagnostic certainty, including active search for alternative cardiac pathologies or non-cardiac causes of dyspnea.

5.3 Combined Biomarker Strategy

A single biomarker is insufficient to capture the systemic pathological complexity and diagnostic heterogeneity of HFpEF. Multi-marker strategies may improve phenotyping and risk stratification, but they should complement, rather than replace, careful clinical evaluation and objective assessment of congestion. Table 2 (Ref. [7,10,12,47,48,49,50,51,52,53]) summarizes the major integrated biomarker combinations that have been investigated in HFpEF, along with their proposed clinical value and key supporting references.

NP + Growth Differentiation Factor 15 (GDF-15): GDF-15, a distant member of the Transforming growth factor beta (TGF-β) family, contributes to disease progression in pathological states and holds significant potential as a therapeutic target in metabolic and cardiovascular disorders. Notably, in a study of heart failure patients with coronary heart disease, GDF-15 levels were found to be higher in HFpEF compared to HFrEF, though GDF-15 is an independent risk factor for adverse outcomes across the entire ejection fraction (EF) spectrum [47].

NP + IL-6: HFpEF is closely linked to low-grade chronic inflammation. In patients with HFpEF, higher interleukin-6 (IL-6) levels were significantly associated with cardiovascular mortality after full multivariable ad-

justment ($p = 0.018$) [50]. These findings suggest that IL-6, particularly when interpreted together with NT-proBNP, may provide useful prognostic information in HFpEF. Although high-sensitivity C-reactive protein (hsCRP) was also evaluated in the original study, it did not reach statistical significance after full adjustment ($p = 0.065$); therefore, its independent prognostic value remains uncertain [50].

NP + Metabolic markers: The integration of NPs with metabolic indicators, including insulin resistance indices, adiponectin, and free fatty acids, is correlated with the metabolism-driven HFpEF subtype [51].

NP + Soluble suppression of tumorigenicity 2 (sST2): sST2 acts as a soluble decoy receptor in the IL-33/ST2 pathway, has been investigated as a circulating marker of myocardial stress and adverse remodeling. In HFpEF patients, higher sST2 levels have been associated with increased 1-year mortality, but its direct relationship to myocardial fibrosis and filling pressure requires further investigation [48].

NP + Myocardial Injury Markers (hs-cTnT): High-sensitivity cardiac troponin T (hs-cTnT) reflects persistent myocardial micro-injury. Adding NT-proBNP to hs-cTnT creates robust prognostic models that improve the prediction of morbidity and mortality across multiple HFpEF cohorts [49].

NP-processing proteases: Corin and furin participate in natriuretic peptide precursor processing through distinct mechanisms. Corin is synthesized as an inactive zymogen and is activated primarily by proprotein convertase subtilisin/kexin type 6 (PCSK6) on the cardiomyocyte surface. Activated corin cleaves proANP and may also contribute to proBNP processing, whereas furin can directly process proBNP into BNP and NT-proBNP. Impaired PCSK6-mediated corin activation disrupts proANP processing and contributes to salt-sensitive hypertension [38,39]. Reduced corin mRNA and protein abundance has also been documented in advanced human systolic heart failure [20]. However, whether these abnormalities specifically contribute to impaired natriuretic peptide processing in HFpEF remains uncertain. Mass spectrometry studies in severe heart failure have demonstrated discrepancies between immunoreactive BNP concentrations and circulating mature BNP-32, suggesting potential abnormalities in NP processing. However, these findings do not establish a comparable degree of processing impairment in HFpEF, and their relevance to this population requires further investigation [18].

6. Therapeutic Strategies Targeting the NP Axis in HFpEF

While the diagnostic utility of NPs in HFpEF is debated, the "functional natriuretic peptide deficiency" hypothesis proposes that the NP axis may represent a therapeutically modifiable target. It is important to note that the mechanistic link between currently available therapies and NP axis restoration in HFpEF remains largely hypothetical; established clinical benefits have been demonstrated through large randomized trials, but whether these benefits operate specifically through NP axis correction is an open question requiring dedicated mechanistic investigation. Rather than positing a total absence of NPs, this framework views HFpEF as a state of systemic imbalance that may be amenable to targeted, phenotype-specific interventions.

6.1 Restoring Signaling: Angiotensin Receptor-Neprilysin Inhibitor (ARNI) in HFpEF

Sacubitril/valsartan, an ARNI, combines neprilysin inhibition with blockade of the angiotensin II type 1 receptor. Although the pivotal PARAGON-HF trial did not meet its primary composite endpoint in the overall HFpEF population, it suggested clinically meaningful benefits in prespecified subgroups, most notably women and patients with left ventricular ejection fraction at or below the median [54]. Further analyses of the PARAGON-HF trial showed that sacubitril/valsartan was associated with reductions in NT-proBNP [55]. This biomarker change is clinically relevant, but whether it reflects restoration of NP-cGMP-PKG signaling, direct effects of neprilysin inhibition on peptide degradation, or concomitant hemodynamic unloading remains mechanistically unresolved in HFpEF.

6.2 Enhancing Downstream cGMP Signaling

Natriuretic peptides mainly exert their effects through activation of natriuretic peptide receptors A and B (NPR-A/B) and the generation of cGMP. Therefore, directly enhancing cGMP signaling is seen as a reasonable approach to bypassing the deficiencies in NP synthesis. Vericiguat, a soluble guanylate cyclase (sGC) stimulator, has demonstrated efficacy in HFrEF [56]. In HFpEF, the SOCRATES-PRESERVED trial did not meet its primary endpoint of NT-proBNP reduction, though exploratory analyses suggested possible improvements in quality of life in certain subgroups [57]. Any benefits in vascular compliance, pulmonary pressure, or exercise tolerance remain hypothesis-generating at this stage and have not been confirmed in adequately powered outcome trials. While large-scale outcome trials have yielded mixed results, the mechanistic rationale for cGMP enhancement in HFpEF remains compelling and warrants further investigation in phenotype-selected populations. On the other hand, phosphodiesterase-5 (PDE5) inhibitors prevent cGMP breakdown. This underscores that enhancing cGMP levels requires phenotype-driven patient selection.

6.3 Indirect Regulation of the NP Axis via Metabolic Modulation

Metabolic-inflammatory states are important contributors to NP axis dysregulation, but currently available therapies should not be interpreted as proven NP-restorative treatments unless this mechanism has been directly demon-

strated. SGLT2 inhibitors reduce the risk of worsening heart failure, including heart-failure hospitalization, in patients with HFpEF or mildly reduced ejection fraction, as demonstrated in the EMPEROR-Preserved and DELIVER trials [58,59]. Their mechanisms are likely multifactorial, including renal tubular effects, preload and afterload reduction, anti-inflammatory actions, and metabolic reprogramming. Regarding GLP-1 receptor agonists, semaglutide improved symptoms and exercise capacity in obese HFpEF phenotypes in STEP-HFpEF [35]. Weight loss may reduce adipose tissue mass and alter NPR-C-mediated NP clearance, but prespecified analyses suggest that NT-proBNP changes may also occur through weight loss-independent pathways. The specific contribution of NP axis modulation to the clinical benefits of GLP-1 receptor agonists therefore remains a hypothesis requiring prospective mechanistic validation.

7. The NP Axis Functional Model and the "Functional NP Deficiency" Hypothesis

HFpEF is a complex systemic syndrome involving variable combinations of diastolic dysfunction, microvascular abnormalities, metabolic stress, inflammation, and comorbid disease. Historically, natriuretic peptides have been viewed as passive biomarkers of ventricular wall tension. However, the dissociation between NP levels and clinical congestion in selected HFpEF populations suggests that concentration-based models are incomplete. In this context, functional NP deficiency is best considered a hypothesis-generating framework that describes imbalance across NP synthesis, processing, clearance, and signaling, rather than a new diagnostic label to be applied to all patients with guideline-defined HFpEF.

7.1 Transitioning From a Concentration-Based to a Functional Model

Traditional research frameworks often assume a near-linear relationship between myocardial wall tension and circulating NP levels. In HFpEF, however, comorbidities such as obesity, insulin resistance, and chronic inflammation may interfere with the transmission of mechanical stretch signals. This can produce remodeling of NP synthesis, processing, clearance, and downstream signaling [10]. The remodeled NP system cannot be fully understood from circulating NP concentrations alone; its biological relevance depends on the clinical context, objective hemodynamics, and downstream tissue responsiveness.

7.2 Concept of Functional NP Deficiency

Based on the pathological characteristics of multi-level dysregulation within the NP axis, functional NP deficiency can be defined as a state in which the core biological effects of the NP system, including natriuresis, vasodilation, and anti-fibrotic signaling, are relatively compromised in relation to the patient's hemodynamic and phenotypic context.

The concept is built upon a body of experimental evidence demonstrating that the NP system in heart failure can fail at multiple levels beyond simple concentration reduction. Hawkridge et al. [18] showed that no mature BNP-32 is detectable in severe heart failure despite high immunoreactive BNP levels, indicating a disconnect between immunoassay results and bioactive peptide. Semenov et al. [19] and Tonne et al. [36] demonstrated that O-glycosylation of proBNP blocks its cleavage by corin and furin, leading to accumulation of less active proBNP. Røsjø et al. [37] confirmed that deglycosylation increases NT-proBNP measurements and improves diagnostic accuracy. Taken together, these findings reveal a key distinction: the NP system may be quantitatively intact or even elevated by immunoassay, yet functionally deficient in terms of bioactive peptide availability and downstream signaling. The term "functional deficiency" is intended to capture this dissociation, rather than to imply absolute depletion of NP peptides.

This concept accommodates several HFpEF phenotypes but should not be used as a universal explanation for all low NP values. In obese HFpEF, low circulating NP concentrations may reflect enhanced adipose-tissue clearance and reduced NP bioavailability; however, they may also reflect limited congestion, treatment-related decongestion, or diagnostic uncertainty [23,25,60]. The framework therefore provides a hypothesis-generating basis for phenotype-based stratification and targeted mechanistic studies, rather than a substitute for established diagnostic algorithms.

To operationalize this concept clinically, we propose the following provisional research criteria for functional NP deficiency in HFpEF: (1) confirmed HFpEF by guideline-supported algorithms, such as Heart Failure Association Pre-test assessment, Echocardiography and natriuretic Peptide score (HFA-PEFF) or H2FPEF, with objective evidence of cardiac structural or functional abnormality; (2) NP levels that are disproportionately low relative to demonstrable congestion or elevated filling pressures, preferably supported by pulmonary artery wedge pressure (PAWP) $\geq$15 mmHg at rest or $\geq$25 mmHg during exercise [7,53]; (3) evidence suggesting at least one axis-level abnormality, including impaired NP synthesis, accelerated peripheral clearance, abnormal proBNP/BNP processing, or reduced downstream cGMP-PKG signaling; and (4) exclusion of alternative explanations, including absence of active congestion, HFpEF mimics, pharmacological effects, renal-function changes, atrial rhythm effects, and non-cardiac causes of dyspnea. These criteria are intended exclusively for research stratification and biomarker validation; they are not suitable for routine clinical diagnosis at this time.

8. Limitations

This review has several limitations. First, as a narrative review rather than a systematic review, our liter-

ature search did not follow a formal PRISMA protocol; the selection and qualitative appraisal of evidence therefore involved interpretive judgment and potential selection bias. Second, much of the mechanistic evidence supporting the "functional NP deficiency" framework, such as impaired proBNP processing, corin dysregulation, and altered glycosylation, derives from severe heart failure populations, HFrEF cohorts, or experimental models, rather than from rigorously phenotyped HFpEF cohorts. Whether and to what extent these mechanisms operate in HFpEF remains unestablished. Third, the diagnostic heterogeneity discussed in Section 5.2 substantially constrains inference at the individual-patient level: a substantial proportion of patients labeled as HFpEF may harbor HFpEF mimics or alternative structural cardiac pathologies, making it unsafe to equate low NP values with intrinsic NP-axis dysfunction in any given case. Fourth, the provisional research criteria proposed in Section 7.2 have not been prospectively validated; they are intended solely as a hypothesis-generating tool for stratification in future studies and should not be applied as diagnostic criteria in clinical practice. Finally, although obesity is central to our discussion of NP suppression, the evidence we synthesize relies predominantly on BMI as the adiposity metric. BMI does not adequately capture visceral adiposity or ectopic fat distribution, which are more closely linked to adverse outcomes in HFpEF.

9. Future Research Directions and Clinical Implications

Despite the emergence of SGLT2 inhibitors and ARNIs as evidence-based therapies, the overall management of HFpEF remains profoundly challenging owing to substantial heterogeneity in treatment response across distinct pathobiological phenotypes. Building upon the NP axis remodeling model, future research must focus on four core pillars: deepening mechanistic understanding, precision phenotyping, optimizing clinical trial design, and translating multidimensional data into clinical guidelines.

Recent evidence highlights the regulatory role of adipokines in HFpEF. These bioactive molecules drive chronic low-grade inflammation, insulin resistance, and endothelial dysfunction, serving as a critical bridge between metabolic abnormality and myocardial distress. To better capture this metabolic risk, future research should utilize advanced metrics, such as the Body Roundness Index (BRI), to more accurately identify patients with high-risk fat distribution and refine HFpEF risk stratification.

Despite these challenges, the NP system should not be regarded as a failed target in HFpEF; rather, it remains a biologically plausible therapeutic axis that requires more precise phenotyping and mechanistic validation. Future research on NP-targeted therapies may include *NPR-C* antagonists designed to reduce peripheral peptide clearance in obesity-related phenotypes, engineered long-acting NP analogues with improved stability or receptor selectivity, and combination strategies that pair ARNIs with SGLT2 inhibitors or downstream cGMP enhancers [60]. These approaches should be tested in phenotype-selected populations with explicit assessment of congestion, NP axis biology, and downstream signaling, rather than being generalized to all HFpEF presentations.

10. Conclusion

The NP system in HFpEF shows complex, context-dependent variation across synthesis, processing, clearance, and signaling. Low NP levels should not be automatically equated with NP axis failure—they may also reflect absence of active congestion, sampling timing, comorbidities, or diagnostic heterogeneity. The concept of functional NP deficiency should therefore be framed as a hypothesis-generating framework for well-phenotyped HFpEF populations, rather than a stand-alone diagnostic entity. Combined biomarker strategies and objective assessment of congestion may provide a more reliable framework for individualized risk stratification and future trials. By integrating mechanistic refinement with careful phenotypic stratification, clinicians and researchers may better address diagnostic ambiguity and improve outcomes for patients with this heterogeneous syndrome.

Author Contributions

XJC contributed to the conception and organization of the review, preparation of the original draft, and conceptual design and development of the figures and tables. IC, WMY, and XLL conceived the review, conducted the literature review and analysis, and contributed significantly to the organization and textual revisions of the article. SGL participated in the analysis and interpretation of the literature relevant to the graphical presentation of the review and contributed to the conceptual design and organization of the figures and tables. SGL also critically reviewed and revised the manuscript for important intellectual content. YLZ participated in the literature review and in the analysis and interpretation of relevant evidence, in addition to contributing to the drafting of the manuscript. All authors reviewed and edited the manuscript for important intellectual content. All authors read and approved the final manuscript and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

Not applicable.

Funding

This work was supported by State Key Laboratory for Innovation and Transformation of Luobing Theory, General Program of National Natural Science Foundation of

China (82370389, 81970339 to XLL, 82400458 to SGL), The National High Technology Research and Development Program of China (2017YFC1700505 to XLL).

Conflicts of Interest

The authors declare no conflicts of interest.

Declaration of AI and AI-Assisted Technologies in the Writing Process

During the preparation of this work, the authors used ChatGPT 5.0 (OpenAI, San Francisco, California, United States) in order to check spelling and grammar. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

References

[1] Mathew D, Elghoul Y, Bhattacharya S, Smith DT. Heart Failure with Preserved Ejection Fraction. The Medical Clinics of North America. 2025; 109: 1175–1195. https://doi.org/10.1016/j.mcna.2025.04.006

[2] Shah SJ, Borlaug BA, Kitzman DW, McCulloch AD, Blaxall BC, Agarwal R, et al. Research Priorities for Heart Failure With Preserved Ejection Fraction: National Heart, Lung, and Blood Institute Working Group Summary. Circulation. 2020; 141: 1001–1026. https://doi.org/10.1161/CIRCULATIONAHA.119.041886

[3] Khan MS, Shahid I, Bennis A, Rakisheva A, Metra M, Butler J. Global epidemiology of heart failure. Nature Reviews. Cardiology. 2024; 21: 717–734. https://doi.org/10.1038/s41569-024-01046-6

[4] Kuwahara K. The natriuretic peptide system in heart failure: Diagnostic and therapeutic implications. Pharmacology & Therapeutics. 2021; 227: 107863. https://doi.org/10.1016/j.pharmthera.2021.107863

[5] Pandit K, Mukhopadhyay P, Ghosh S, Chowdhury S. Natriuretic peptides: Diagnostic and therapeutic use. Indian Journal of Endocrinology and Metabolism. 2011; 15: S345–S353. https://doi.org/10.4103/2230-8210.86978

[6] Samad M, Malempati S, Restini CBA. Natriuretic Peptides as Biomarkers: Narrative Review and Considerations in Cardiovascular and Respiratory Dysfunctions. The Yale Journal of Biology and Medicine. 2023; 96: 137–149. https://doi.org/10.59249/NCST6937

[7] Pieske B, Tschöpe C, de Boer RA, Fraser AG, Anker SD, Donal E, et al. How to diagnose heart failure with preserved ejection fraction: the HFA-PEFF diagnostic algorithm: a consensus recommendation from the Heart Failure Association (HFA) of the European Society of Cardiology (ESC). European Heart Journal. 2019; 40: 3297–3317. https://doi.org/10.1093/eurheartj/ehz641

[8] Borlaug BA, Redfield MM. Diastolic and systolic heart failure are distinct phenotypes within the heart failure spectrum. Circulation. 2011; 123: 2006–2014. https://doi.org/10.1161/CIRCULATIONAHA.110.954388

[9] Cai Z, Wu C, Xu Y, Cai J, Zhao M, Zu L. The NO-cGMP-PKG Axis in HFpEF: From Pathological Mechanisms to Potential Therapies. Aging and Disease. 2023; 14: 46–62. https://doi.org/10.14336/AD.2022.0523

[10] Tsutsui H, Albert NM, Coats AJS, Anker SD, Bayes-Genis A, Butler J, et al. Natriuretic peptides: role in the diagnosis and management of heart failure: a scientific statement from the Heart Failure Association of the European Society of Cardiology, Heart Failure Society of America and Japanese Heart Failure Society. European Journal of Heart Failure. 2023; 25: 616–631. https://doi.org/10.1002/ejhf.2848

[11] Chen YY, Liang L, Tian PC, Feng JY, Huang LY, Huang BP, et al. Clinical characteristics and outcomes of patients hospitalized with heart failure with preserved ejection fraction and low NT-proBNP levels. Medicine. 2023; 102: e36351. https://doi.org/10.1097/MD.0000000000036351

[12] Ammar LA, Massoud GP, Chidiac C, Booz GW, Altara R, Zouein FA. BNP and NT-proBNP as prognostic biomarkers for the prediction of adverse outcomes in HFpEF patients: A systematic review and meta-analysis. Heart Failure Reviews. 2025; 30: 45–54. https://doi.org/10.1007/s10741-024-10442-6

[13] Khan AM, Cheng S, Magnusson M, Larson MG, Newton-Cheh C, McCabe EL, et al. Cardiac natriuretic peptides, obesity, and insulin resistance: evidence from two community-based studies. The Journal of clinical endocrinology and metabolism. 2011; 96: 3242–3249. https://doi.org/10.1210/jc.2011-1182

[14] Bordicchia M, Ceresiani M, Pavani M, Minardi D, Polito M, Wabitsch M, et al. Insulin/glucose induces natriuretic peptide clearance receptor in human adipocytes: a metabolic link with the cardiac natriuretic pathway. American Journal of Physiology. Regulatory, Integrative and Comparative Physiology. 2016; 311: R104–R114. https://doi.org/10.1152/ajpregu.00499.2015

[15] Lam CS, Rienstra M, Tay WT, Liu LC, Hummel YM, van der Meer P, et al. Atrial Fibrillation in Heart Failure With Preserved Ejection Fraction: Association With Exercise Capacity, Left Ventricular Filling Pressures, Natriuretic Peptides, and Left Atrial Volume. JACC. Heart failure. 2017; 5: 92–98. https://doi.org/10.1016/j.jchf.2016.10.005

[16] Tsutamoto T, Sakai H, Yamamoto T, Nakagawa Y. Renal Clearance of N-Terminal pro-Brain Natriuretic Peptide Is Markedly Decreased in Chronic Kidney Disease. Circulation Reports. 2019; 1: 326–332. https://doi.org/10.1253/circrep.CR-19-0063

[17] Chirinos JA, Orlenko A, Zhao L, Basso MD, Cvijic ME, Li Z, et al. Multiple Plasma Biomarkers for Risk Stratification in Patients With Heart Failure and Preserved Ejection Fraction. Journal of the American College of Cardiology. 2020; 75: 1281–1295. https://doi.org/10.1016/j.jacc.2019.12.069

[18] Hawkridge AM, Heublein DM, Bergen HR, 3rd, Cataliotti A, Burnett JC, Jr, Muddiman DC. Quantitative mass spectral evidence for the absence of circulating brain natriuretic peptide (BNP-32) in severe human heart failure. Proceedings of the National Academy of Sciences of the United States of America. 2005; 102: 17442–17447. https://doi.org/10.1073/pnas.0508782102

[19] Semenov AG, Postnikov AB, Tamm NN, Seferian KR, Karpova NS, Bloshchitsyna MN, et al. Processing of pro-brain natriuretic peptide is suppressed by O-glycosylation in the region close to the cleavage site. Clinical Chemistry. 2009; 55: 489–498. https://doi.org/10.1373/clinchem.2008.113373

[20] Lee R, Xu B, Rame JE, Felkin LE, Barton P, Dries DL. Regulated inositol-requiring protein 1-dependent decay as a mechanism of corin RNA and protein deficiency in advanced human systolic heart failure. Journal of the American Heart Association. 2014; 3: e001104. https://doi.org/10.1161/JAHA.114.001104

[21] 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: 263–271. https://doi.org/10.1016/j.jacc.2013.02.092

[22] Hahn VS, Knutsdottir H, Peterson TE, Kikuchi D, Vungarala S, Kass DA, et al. Relationship Between Myocardial NPPB Expression and Serum NT-proBNP in Heart Failure With Preserved

Ejection Fraction. JACC. Heart Failure. 2024; 12: 1306–1308. https://doi.org/10.1016/j.jchf.2024.02.027
[23] Clerico A, Giannoni A, Vittorini S, Emdin M. The paradox of low BNP levels in obesity. Heart Failure Reviews. 2012; 17: 81–96. https://doi.org/10.1007/s10741-011-9249-z
[24] Gentili A, Frangione MR, Albini E, Vacca C, Ricci MA, De Vuono S, et al. Modulation of natriuretic peptide receptors in human adipose tissue: molecular mechanisms behind the "natriuretic handicap" in morbidly obese patients. Translational research. 2017; 186: 52–61. https://doi.org/10.1016/j.trsl.2017.06.001
[25] Obokata M, Reddy YNV, Pislaru SV, Melenovsky V, Borlaug BA. Evidence Supporting the Existence of a Distinct Obese Phenotype of Heart Failure With Preserved Ejection Fraction. Circulation. 2017; 136: 6–19. https://doi.org/10.1161/CIRCULATIONAHA.116.026807
[26] Zhang H, Thoonen R, Yao V, Buys ES, Popovich J, Su YR, et al. Regulation of B-type natriuretic peptide synthesis by insulin in obesity in male mice. Experimental Physiology. 2016; 101: 113–123. https://doi.org/10.1113/EP085091
[27] Ostrominski JW, Neuen BL, Claggett BL, Anand IS, Desai AS, Jhund PS, et al. Natriuretic Peptides, Body Mass Index, and Clinical Outcomes in Heart Failure With Mildly Reduced or Preserved Ejection Fraction. Journal of the American College of Cardiology. 2025; 86: 1823–1839. https://doi.org/10.1016/j.jacc.2025.08.028
[28] Wang TJ, Larson MG, Levy D, Benjamin EJ, Leip EP, Wilson PW, et al. Impact of obesity on plasma natriuretic peptide levels. Circulation. 2004; 109: 594–600. https://doi.org/10.1161/01.CIR.0000112582.16683.EA
[29] Das SR, Drazner MH, Dries DL, Vega GL, Stanek HG, Abdullah SM, et al. Impact of body mass and body composition on circulating levels of natriuretic peptides: results from the Dallas Heart Study. Circulation. 2005; 112: 2163–2168. https://doi.org/10.1161/CIRCULATIONAHA.105.555573
[30] Selvaraj S, Kim J, Ansari BA, Zhao L, Cvijic ME, Fronheiser M, et al. Body Composition, Natriuretic Peptides, and Adverse Outcomes in Heart Failure With Preserved and Reduced Ejection Fraction. JACC. Cardiovascular Imaging. 2021; 14: 203–215. https://doi.org/10.1016/j.jcmg.2020.07.022
[31] Fu K, Dong Y, Wang Z, Teng J, Cheng C, Su C, et al. The role of body composition in left ventricular remodeling, reverse remodeling, and clinical outcomes for heart failure with mildly reduced ejection fraction: more knowledge to the "obesity paradox". Cardiovascular Diabetology. 2024; 23: 334. https://doi.org/10.1186/s12933-024-02430-9
[32] Pugliese NR, Paneni F, Tricò D, Bacca AV, De Biase N, Dalpiaz H, et al. Refining the link between obesity and heart failure: insights from GLP-1 receptor agonist trials and studies adopting direct adiposity measures. Cardiovascular Diabetology. 2025; 24: 224. https://doi.org/10.1186/s12933-025-02778-6
[33] Brachs M, Wiegand S, Leupelt V, Ernert A, Kintscher U, Jumpertz von Schwarzenberg R, et al. ANP system activity predicts variability of fat mass reduction and insulin sensitivity during weight loss. Metabolism: Clinical and Experimental. 2016; 65: 935–943. https://doi.org/10.1016/j.metabol.2016.03.013
[34] Poh KK, Shabbir A, Ngiam JN, Lee PSS, So J, Frampton CM, et al. Plasma Clearance of B-Type Natriuretic Peptide (BNP) before and after Bariatric Surgery for Morbid Obesity. Clinical Chemistry. 2021; 67: 662–671. https://doi.org/10.1093/clinchem/hvaa308
[35] Butler J, Shah SJ, Petrie MC, Borlaug BA, Abildstrøm SZ, Davies MJ, et al. Semaglutide versus placebo in people with obesity-related heart failure with preserved ejection fraction: a pooled analysis of the STEP-HFpEF and STEP-HFpEF DM randomised trials. Lancet. 2024; 403: 1635–1648. https://doi.org/10.1016/S0140-6736(24)00469-0
[36] Tonne JM, Campbell JM, Cataliotti A, Ohmine S, Thatava T, Sakuma T, et al. Secretion of glycosylated pro-B-type natriuretic peptide from normal cardiomyocytes. Clinical Chemistry. 2011; 57: 864–873. https://doi.org/10.1373/clinchem.2010.157438
[37] Røsjø H, Dahl MB, Jørgensen M, Røysland R, Brynildsen J, Cataliotti A, et al. Influence of glycosylation on diagnostic and prognostic accuracy of N-terminal pro-B-type natriuretic peptide in acute dyspnea: data from the Akershus Cardiac Examination 2 Study. Clinical Chemistry. 2015; 61: 1087–1097. https://doi.org/10.1373/clinchem.2015.239673
[38] Chen S, Cao P, Dong N, Peng J, Zhang C, Wang H, et al. PCSK6-mediated corin activation is essential for normal blood pressure. Nature medicine. 2015; 21: 1048–1053. https://doi.org/10.1038/nm.3920
[39] Semenov AG, Tamm NN, Seferian KR, Postnikov AB, Karpova NS, Serebryanaya DV, et al. Processing of pro-B-type natriuretic peptide: furin and corin as candidate convertases. Clinical Chemistry. 2010; 56: 1166–1176. https://doi.org/10.1373/clinchem.2010.143883
[40] Hamdani N, Franssen C, Lourenço A, Falcão-Pires I, Fontoura D, Leite S, et al. Myocardial titin hypophosphorylation importantly contributes to heart failure with preserved ejection fraction in a rat metabolic risk model. Circulation. Heart Failure. 2013; 6: 1239–1249. https://doi.org/10.1161/CIRCHEARTFAILURE.113.000539
[41] Mohammed SF, Hussain S, Mirzoyev SA, Edwards WD, Maleszewski JJ, Redfield MM. Coronary microvascular rarefaction and myocardial fibrosis in heart failure with preserved ejection fraction. Circulation. 2015; 131: 550–559. https://doi.org/10.1161/CIRCULATIONAHA.114.009625
[42] Thorp EB, Filipp M. Contributions of Inflammation to Cardiometabolic Heart Failure with Preserved Ejection Fraction. Annual Review of Pathology. 2025; 20: 143–167. https://doi.org/10.1146/annurev-pathmechdis-111523-023405
[43] Packer M. The Adipokine Hypothesis of Heart Failure With a Preserved Ejection Fraction: A Novel Framework to Explain Pathogenesis and Guide Treatment. Journal of the American College of Cardiology. 2025; 86: 1269–1373. https://doi.org/10.1016/j.jacc.2025.06.055
[44] Verbrugge FH, Omote K, Reddy YNV, Sorimachi H, Obokata M, Borlaug BA. Heart failure with preserved ejection fraction in patients with normal natriuretic peptide levels is associated with increased morbidity and mortality. European Heart Journal. 2022; 43: 1941–1951. https://doi.org/10.1093/eurheartj/ehab911
[45] Bellicini MG. HFpEF and HFmrEF in acute heart failure: isolated diastolic dysfunction or alternative cardiac pathologies? Internal and Emergency Medicine. 2025; 20: 2389–2392. https://doi.org/10.1007/s11739-025-04097-w
[46] Landsteiner I, Verwerft J, Belov D, Verbrugge FH, Lewis GD. Heart failure and preserved ejection fraction: pathophysiology, clinical assessment, and management of exercise intolerance. European Heart Journal. 2026; 47: 3065–3101. https://doi.org/10.1093/eurheartj/ehag175
[47] Lyu L, Xu J, Xv C, Xiao H, Liu Z, He Y, et al. Prognostic value of growth differentiation factor-15 in heart failure among whole ejection fraction phenotypes. ESC Heart Failure. 2024; 11: 2295–2304. https://doi.org/10.1002/ehf2.14807
[48] Shah KB, Kop WJ, Christenson RH, Diercks DB, Henderson S, Hanson K, et al. Prognostic utility of ST2 in patients with acute dyspnea and preserved left ventricular ejection fraction. Clinical Chemistry. 2011; 57: 874–882. https://doi.org/10.1373/clinchem.2010.159277
[49] Pocock SJ, Ferreira JP, Packer M, Zannad F, Filippatos G, Kondo T, et al. Biomarker-driven prognostic models in chronic

heart failure with preserved ejection fraction: the EMPEROR-Preserved trial. European Journal of Heart Failure. 2022; 24: 1869–1878. https://doi.org/10.1002/ejhf.2607

[50] Berger M, März W, Niessner A, Delgado G, Kleber M, Scharnagl H, et al. IL-6 and hsCRP predict cardiovascular mortality in patients with heart failure with preserved ejection fraction. ESC Heart Failure. 2024; 11: 3607–3615. https://doi.org/10.1002/ehf2.14959

[51] Campbell P, Rutten FH, Lee MM, Hawkins NM, Petrie MC. Heart failure with preserved ejection fraction: everything the clinician needs to know. Lancet. 2024; 403: 1083–1092. https://doi.org/10.1016/S0140-6736(23)02756-3

[52] Reddy YNV, Tada A, Obokata M, Carter RE, Kaye DM, Handoko ML, et al. Evidence-Based Application of Natriuretic Peptides in the Evaluation of Chronic Heart Failure With Preserved Ejection Fraction in the Ambulatory Outpatient Setting. Circulation. 2025; 151: 976–989. https://doi.org/10.1161/CIRCULATIONAHA.124.072156

[53] McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. European Heart Journal. 2021; 42: 3599–3726. https://doi.org/10.1093/eurheartj/ehab368

[54] Solomon SD, McMurray JJV, Anand IS, Ge J, Lam CSP, Maggioni AP, et al. Angiotensin-Neprilysin Inhibition in Heart Failure with Preserved Ejection Fraction. The New England Journal of Medicine. 2019; 381: 1609–1620. https://doi.org/10.1056/NEJMoa1908655

[55] Cunningham JW, Vaduganathan M, Claggett BL, Zile MR, Anand IS, Packer M, et al. Effects of Sacubitril/Valsartan on N-Terminal Pro-B-Type Natriuretic Peptide in Heart Failure With Preserved Ejection Fraction. JACC. Heart Failure. 2020; 8: 372–381. https://doi.org/10.1016/j.jchf.2020.03.002

[56] Armstrong PW, Pieske V, Anstrom KJ, Ezekowitz J, Hernandez AF, Butler J, et al. Vericiguat in Patients with Heart Failure and Reduced Ejection Fraction. The New England Journal of Medicine. 2020; 382: 1883–1893. https://doi.org/10.1056/NEJMoa1915928

[57] Pieske B, Maggioni AP, Lam CSP, Pieske-Kraigher E, Filippatos G, Butler J, et al. Vericiguat in patients with worsening chronic heart failure and preserved ejection fraction: results of the SOluble guanylate Cyclase stimulatoR in heArT failurE patientS with PRESERVED EF (SOCRATES-PRESERVED) study. European Heart Journal. 2017; 38: 1119–1127. https://doi.org/10.1093/eurheartj/ehw593

[58] Anker SD, Butler J, Filippatos G, Ferreira JP, Bocchi E, Böhm M, et al. Empagliflozin in Heart Failure with a Preserved Ejection Fraction. The New England Journal of Medicine. 2021; 385: 1451–1461. https://doi.org/10.1056/NEJMoa2107038

[59] Solomon SD, McMurray JJV, Claggett B, de Boer RA, DeMets D, Hernandez AF, et al. Dapagliflozin in Heart Failure with Mildly Reduced or Preserved Ejection Fraction. The New England Journal of Medicine. 2022; 387: 1089–1098. https://doi.org/10.1056/NEJMoa2206286

[60] Egom EEA. Natriuretic Peptide Clearance Receptor (NPR-C) Pathway as a Novel Therapeutic Target in Obesity-Related Heart Failure With Preserved Ejection Fraction (HFpEF). Frontiers in Physiology. 2021; 12: 674254. https://doi.org/10.3389/fphys.2021.674254