Review Article

The Role of Biomarkers in Heart Failure with Preserved Ejection Fraction

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Introduction

A large proportion of patients with heart failure (HF) have preserved left ventricle (LV) ejection fraction (HFpEF)[1] or slightly reduced systolic function. Although specific cutoff recommendations are constantly evolving, the European Society of Cardiology (ESC) has recently proposed the term HF with mildly reduced ejection fraction (HFmrEF) for values between 40–49% and HFpEF for ejection fraction ≥ 50%.[2] In the past, different cutoffs were used in studies of HFpEF, ranging from 40% to 55%. Additionally, there is significant overlap between HFpEF and HFmrEF. For these reasons, in this chapter we consider them as a whole.

HFpEF is associated with many comorbidities and has a high rate of morbidity and mortality, both in ambulatory and in-hospital cohorts.[3-5] HFpEF is a heterogeneous syndrome with diverse etiologies and phenotypes and different pathophysiological pathways, which are not fully understood.[6,7] Circulating biomarkers may represent important tools to aid in the diagnosis and prognosis of this condition.[8,9]

In this review, we discuss the role of biomarkers that reflect different pathological pathways in HFpEF, with most attention given to myocardial stretch and injury biomarkers such as natriuretic peptides (NP) and troponin. We also provide an overview of biomarkers of inflammation, oxidative stress, fibrosis, and vascular dysfunction.

Natriuretic peptides

NP are endogenous hormones with a variety of hemodynamic, renal, and neurohormonal effects. They are considered the gold standard biomarkers in HF and are secreted almost exclusively by the heart. Although the role of NP has been more extensively demonstrated in patients with reduced ejection fraction (HFrEF), their clinical value has been shown across the whole spectrum of ejection fraction.[10-12] However, the mean concentrations are lower in patients with HFpEF than in those with HFrEF.[13,14] Nevertheless, a specific cutoff does not exist to differentiate HFpEF from HFrEF due to significant overlapping.[14]

NP are mainly released in response to myocardial wall stress, leading to an elevation of LV filling pressures (Figure 1). The NP of most clinical importance are B-type natriuretic peptide (BNP) and N-terminal proBNP (NT-proBNP). Other NP such as atrial natriuretic peptide (ANP), N-terminal proANP, and C-type NP (CNP), although of importance in terms of pathophysiology, have not been used in clinical practice due to the complex logistics required for their measurement.

Diagnosis of HFpEF

The role of NP in the diagnosis of HF, including HFpEF, has been examined in several reports, both in acute and chronic settings.[1,13,15-21] Villacorta et al.[13] and Maisel et al.[15] (in initial studies in the acute setting with BNP)[13,15] and Januzzi et al. (with NT-proBNP)[16] demonstrated good accuracy for the diagnosis of HF in the entire spectrum of ejection fraction. More recently, Januzzi et al. have confirmed the findings for NT-proBNP in the ICON-RELOADED study.[17] In this study, 41.3% of patients with a diagnosis of acute HF had an LV ejection fraction ≥ 50%. The negative predictive value for NT-proBNP was excellent, close to 98%. In the non-acute setting, Tschöpe et al., in a study with 68 patients with diastolic dysfunction, found that NT-proBNP levels were significantly elevated as compared to those of healthy controls and correlated well with invasive measurements of LV filling pressures.[19] Jorge et al., in a population-based study, found that BNP < 42 pg/mL had a sensitivity of 92% and a negative predictive value of 99% for the diagnosis of HF, regardless of

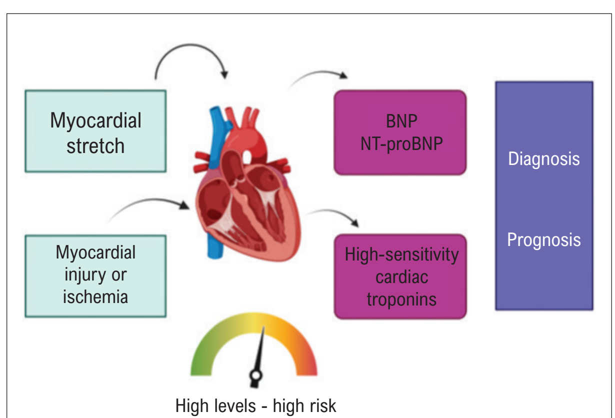

Figure 1 – *Standard cardiac biomarkers in HFpEF: NT-proBNP and hs-cTn. NT-proBNP: N-terminal pro-B-type natriuretic peptide.*

Keywords

Heart failure; Preserved Ejection Fraction; Biomarkers.

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the ejection fraction. In this study, 59% of the population with HF had HFpEF. A recent meta-analysis of 51 studies found that NP have reasonable diagnostic performance in the detection of HFpEF in the non-acute setting, with an area under the curve (AUC) of 80%.[21] The best utility of these markers was for ruling out diastolic dysfunction or HFpEF, with a negative predictive value of 85%. The specificity and positive predictive value, however, were poor (65% and 60%, respectively).

In all studies mentioned above, patients with HFpEF had lower values of NP than patients with HFrEF. A possible explanation for this could be a stronger association of NP with end-diastolic wall stress, which is lower in HFpEF than in HFrEF.[22]

Although NP have been proved to be a good tool for the diagnosis of HFpEF, there are some caveats. NP are influenced by many cardiac and non-cardiac disorders that seem to be even more important in HFpEF. Increased levels of NP are expected in atrial fibrillation, older adults, and those with renal dysfunction. A fivefold increase in NT-proBNP has been reported in patients with HFpEF and atrial fibrillation compared to those in sinus rhythm.[23] In contrast, lower values are observed in obese patients.[12]

All of these characteristics are common in patients with HFpEF, which could explain the unexpected results observed in some studies. For example, Arjan et al. found that 29% of symptomatic outpatients with HFpEF and elevated pulmonary wedge pressures had "normal" BNP values (< 100 pg/mL), suggesting that a normal BNP level may not exclude the diagnosis of HFpEF.[24] More recently, Verbrugge et al. observed similar results.[25] Using invasive hemodynamics, they retrospectively compared patients with HFpEF and high NT-proBNP values (≥ 125 pg/mL), HFpEF and normal NT-proBNP values (< 125 pg/mL), and a third group of controls with normal hemodynamics. Patients with HFpEF and normal NP (37% of the population with HF) were younger than those in the high NP group, had a higher rate of obesity, and had less structural heart diseases as assessed by echocardiography. The highest event rate was observed in the group with high NP values, but patients with normal NT-proBNP still had a 2.7-fold higher risk for mortality or HF readmission compared with controls. The limitations of the study were its retrospective nature and the fact that it was performed with patients referred to a tertiary center for invasive hemodynamic tests, possibly causing a referral bias.

Due to the reduced performance of biomarkers in some subgroups of patients (the ones mentioned above), some authors have used machine learning techniques, combining clinical variables with biomarkers as a continuous variable in an effort to improve diagnostic accuracy. This strategy has been successfully used for the diagnosis of acute myocardial infarction using high-sensitivity troponins[26] and for the diagnosis of pulmonary embolism using D-dimer.[27] Recently, Lee et al. developed a model named CoDE-HF, which used machine learning techniques to overcome the barriers observed in some subgroups due to the influence of clinical variables on the diagnostic performance of NT-proBNP.[28] They combined the biomarker with ten clinical variables. This tool ruled in and ruled out acute heart failure more accurately than did any approach using NT-proBNP thresholds alone and performed consistently across all subgroups.

HFpEF is a complex disease whose pathophysiology is poorly understood, and its diagnosis is difficult to establish. To simplify the diagnostic approach for the clinician, clinical scores were created. The two most used are the H_2FPEF score,[29] developed by the Mayo Clinic, and the HFA-PEFF score, created by the ESC.[30] An important difference between these two scores is that the H_2FPEF score does not include biomarkers. In contrast, the HFA-PEFF score incorporates NP. Both scores are recommended by the main HF guidelines, with no preference of one over the other.[2,31,32] In the external validation of H_2FPEF,[33] the score had a poor performance in patients presenting with dyspnea. On the contrary, HFA-PEFF demonstrated good accuracy in the validation cohort.[34] Of note, the biomarker domain performed almost as well as the whole score (AUC 89% vs 90%, respectively). However, 3 out of 11 patients classified in the low-probability category still had HFpEF, underscoring the relatively low sensitivity of the score. A prospective head-to-head comparison between the two scores is lacking. In this regard, only one case-control study has been carried out.[35] In this investigation, both scores discriminated patients with HFpEF from controls, but the H_2FPEF score had a greater AUC (84% vs 71%). Specificity was robust for both scores, but sensitivity was poorer for HFA-PEFF (false-negative rate of 55% for low-probability scores compared with 25% for H_2FPEF). However, these results should be interpreted with caution due to the retrospective nature of the study.

Prognosis of HFpEF

The usefulness of NP goes beyond their diagnostic role. The higher the values, the higher the event rates. In the acute setting, NT-proBNP is considered a strong independent predictor of all-cause mortality, as described in the study by Lopuszynski et al. performed in a cohort hospitalized with HFpEF.[36] Admission and discharge levels and relative changes during hospitalization confer the same relative risk information for HFpEF as in HFrEF.[37]

In chronic HF, several studies have shown that NP provide strong and independent prognostic information.[38-41] In the I-PRESERVE Study, NT-proBNP emerged as one of the strongest predictors of all-cause mortality or cardiovascular hospitalization.[39] There was a continuous linear increase in the incidence of the primary endpoint from the lowest to the highest quartiles of NT-proBNP.[40] A recent unsupervised cluster analysis based on a wide range of biomarkers found that higher levels of NT-proBNP identify a subgroup of HFpEF patients (who also have higher levels of cardiac troponins) who are at the highest risk of death or HF hospitalization.[41]

Guiding Therapy in HFpEF

Although there is a suggestion that NP may be helpful in guiding therapy in patients with HFrEF, few studies have examined this issue in patients with HFpEF. Maeder et al.[42] studied 123 patients with HFpEF (ejection fraction > 45%) who were randomized to standard medical therapy, titrated to reduce symptoms to NYHA class ≤ II or also to reduce NT-proBNP below the inclusion threshold (400 or 800 pg/mL, depending on age). Differently from patients with HFrEF, patients with HFpEF did not benefit from this strategy. In fact, NP-guided therapy tended to worsen 18-month outcomes in patients with HFpEF. This finding was later confirmed in a meta-analysis performed by Brunner-La Roca et al.[43] In contrast, patients with the so-called "mid-range" ejection fraction, now referred to as mildly reduced ejection fraction, seemed to have the same benefits with NP-guided therapy as patients with HFrEF. Rickenbach et al.,[44] using data from the TIME-CHF trial, demonstrated a benefit of NT-proBNP-guided therapy regarding survival free of HF hospitalization in HFrEF and HFmrEF, but not in HFpEF.

High-sensitivity cardiac troponins

Traditionally used in the diagnosis of acute myocardial infarction, cardiac troponins are now being increasingly detected in HF due to improvements in assay sensitivity. This is referred to as myocardial injury (acute or chronic).[11] Values of cardiac troponins in HF may be elevated in the whole spectrum of ejection fraction but are higher in HFrEF compared to HFpEF.[45] Elevated high-sensitivity cardiac troponin (hs-cTn) discriminates a subgroup of patients with HFpEF who have ongoing myocardial damage, higher wall stress, or impaired microcirculation, as evidenced in a mechanistic study performed by Obokata et al.[46]. They compared 38 patients with HFpEF with 20 control patients. Those with HFpEF had higher troponin levels at rest, which correlated with higher pulmonary capillary wedge pressure and worse systolic and diastolic tissue Doppler velocities. Additionally, troponins correlated with a greater degree of oxygen supply-demand mismatch.

Baseline hs-cTn has been shown to predict HFpEF in older adults, especially in those without LV hypertrophy at baseline.[47] There was a 2.4-fold increase in the incidence of HFpEF in patients in the third tertile of troponin compared with patients in the first tertile. In the acute setting, several studies have shown a prognostic role of hs-cTn measured at admission or discharge in patients hospitalized with decompensated HFpEF.[48-50]

Both hs-cTn T and I are elevated in chronic HFpEF and are independently associated with poorer outcomes.[11,12,51] In the study by Gohar et al.[51], the hs-cTn T assay provided the greatest additional prognostic value in HFpEF in comparison with hs-cTn I and NT-proBNP. However, hs-cTn I was more strongly associated with composite events in men with HFpEF.

Serial measurements of hs-cTn in patients with HFpEF have also been studied. In a substudy of the PARAGON-HF trial, investigators demonstrated that hs-cTn T was reduced by sacubitril/valsartan therapy compared to valsartan and that patients with a decrease in hs-cTn T (from randomization to 16 weeks to a value at or below the median value of 17 ng/L) subsequently had a lower risk of the composite outcome than those who had persistently elevated hs-cTn T values.[52] Thus, both baseline and serial measurements of hs-cTn seem to be useful to predict events in patients with HFpEF. Figure 1 illustrates the stimulus for hs-cTn release and its role in clinical practice in HFpEF.

Other biomarkers

NP and hs-cTn are standard and established cardiac biomarkers. Their accuracy in the diagnosis and prognosis of cardiovascular conditions in great part results from the fact that they are secreted almost exclusively by the heart. However, heart diseases have systemic repercussions and are influenced by systemic conditions as well. In this regard, there is a potential role for systemic biomarkers in HFpEF, which are driven by different pathways (Figure 2). These markers are not useful for diagnosis, since they are not specific for the heart, but are important prognostic markers.

GDF-15

Growth differentiation factor-15 (GDF-15) is a member of the transforming growth factor-β cytokine superfamily associated with inflammation and oxidative stress.[53] It has emerged as a useful marker in many cardiovascular conditions, such as coronary artery disease, atrial fibrillation, and HF, and also in non-cardiac disorders such as obesity and COVID-19.[53] GDF-15 is elevated in patients with HFpEF and provides additional prognostic information over clinical variables and traditional biomarkers.[54,55] Izumiya et al.[54] demonstrated a positive association of GDF-15 with NYHA class and BNP, and GDF-15 strongly predicted cardiovascular events. Interesting findings were also observed by Santhanakrishnan et al.[55]. They compared different biomarkers in HFrEF vs HFpEF and their relation to each other. GDF-15 strongly differentiated HFpEF cases from healthy controls and the NT-proBNP/GDF-15 ratio distinguished between HFrEF and HFpEF. This finding is consistent with the important role of inflammation in HFpEF.

Many patients with HFpEF have atrial fibrillation and an important role of GDF-15 in this scenario has been

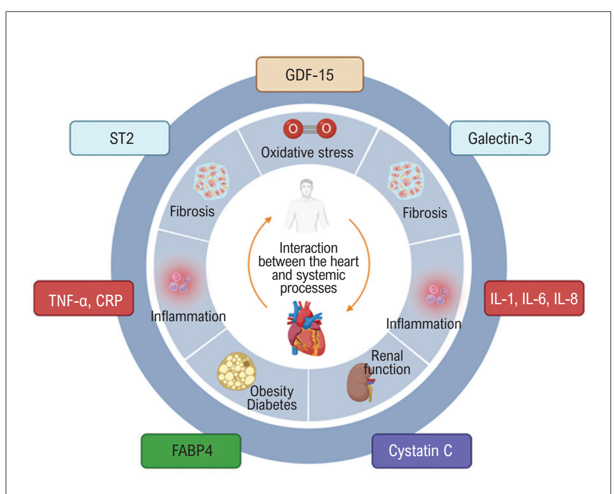

Figure 2 – *Systemic biomarkers involved in HFpEF, addressing the relationship of systemic processes and the heart. CRP: C-reactive protein; FABP4: fatty acid-binding protein 4; GDF-15: growth differentiation factor 15; IL: interleukin; ST2: suppression of tumorigenicity 2; TNF: tumor necrosis factor.*

demonstrated.[56-58] GDF-15 is the strongest predictor of bleeding in patients with atrial fibrillation taking anticoagulants.[56] The ABC (age, biomarker, clinical history) score is a biomarker-based risk score developed for the prediction of stroke and bleeding in patients with atrial fibrillation. The ABC bleeding score[56] incorporates GDF-15 and hs-cTn, and the ABC stroke score[57] incorporates NP and hs-cTn. Both ABC scores outperformed the traditional risk scores in atrial fibrillation (ABC bleeding and HAS-BLED, AUC 0.69 vs 0.62, respectively; ABC stroke and CHADSVASC, AUC 0.67 vs 0.59, respectively).[58]

Thus, GDF-15 is a promising biomarker in HFpEF. In addition to the prognostic role, it may contribute to elucidating the pathophysiology of HFpEF and identifying specific target therapies.

ST2

ST2 is a member of the interleukin 1 receptor family, also known as interleukin 1 receptor-like 1 (IL1RL-1).[59] ST2 stands for "suppression of tumorigenicity 2". ST2 is the receptor for interleukin-33 (IL-33), which exerts its effects by binding to the transmembrane receptor ST2L isoform, anchored in the myocyte membrane. The interaction of IL-33 and ST2L has been proven to be cardioprotective in experimental models, reducing myocardial fibrosis, cardiomyocyte hypertrophy, and apoptosis and improving myocardial function. However, the soluble ST2 receptor (sST2) works as a decoy receptor, which inhibits ST2L binding to IL-33. For this reason, sST2 has been proposed as a marker of cardiac hypertrophy, fibrosis, and remodeling.[59]

In HFpEF, ST2 release may be related to myocardial stress and an elevated LV filling pressure, as demonstrated by the direct correlation of ST2 levels with the diastolic load measured on the basis of the LV end diastolic pressure.[60,61] The TIME-CHF study measured circulating levels of different biomarkers and sST2 levels were higher in patients with HFpEF compared to those with HfrEF.[45] In patients presenting with acute dyspnea and normal LV systolic function, ST2 was the only biomarker predicting mortality.[62] These results were also observed in the study by Manzano-Fernandes et al. in acutely decompensated HF, where the prognostic value of ST2 in HFpEF was comparable to that in HFrEF.[63] These findings suggest that ST2 may be a useful prognostic marker in HFpEF, especially in the acute setting.

Galectin-3

Galectin-3 (Gal-3) has also been mechanistically involved in cardiovascular inflammation and fibrosis.[11] In the PARAMOUNT trial, Gal-3 correlated with disease severity as evidenced by the positive correlation with NT-proBNP and the E/E' ratio in patients with HFpEF.[64] In a study with 592 patients, Gal-3 was a stronger predictor of mortality in patients with HFpEF compared to those with HFrEF.[65] In addition, serial measurements of GAL-3 seem to be valuable. In the ALDO-DHF trial, increases in Gal-3 over time were associated with all-cause mortality.[66] Finally, Gal-3 can predict the development of HFpEF in patients with comorbidities (de Boer 2013).[67]

Inflammatory markers

Elevated levels of inflammatory cytokines such as TNF-α, IL1, IL6, IL8, and CRP are often observed in patients with HFpEF.[10] Circulating levels of TNF-α receptors (TNFR1 and TNFR2) are associated with the severity of diastolic dysfunction and symptoms.[10] Nevertheless, scarce evidence on their prognostic role is currently available.

Fatty acid-binding protein 4

Fatty acid-binding proteins (FABPs) are intracellular lipid chaperones.[12] FABP4—also known as adipocyte FABP or aP2—plays an important role in the development of obesity, insulin resistance, diabetes, and atherosclerosis and has been associated with cardiac remodeling and left and right ventricular dysfunction.[68,69] In a substudy of the TOPCAT trial, FAPB4 was associated with the risk of death or HF admission in HFpEF, independently of the MAGGIC risk score.[70] Recently, Harada et al. reported that event-free survival was significantly decreased in patients with HFpEF and FABP4 ≥ 43.5 ng/mL.[69]

Cystatin C

Cystatin C is secreted by nucleated cells at a constant rate, filtered and reabsorbed by the glomeruli, and then completely decomposed by intact renal tubules; it provides a more accurate method for estimated glomerular filtration rate (eGFR) measurement.[12] Excess cystatin C may promote myocardial fibrosis and ventricular hypertrophy and increase atrial volume.[12] It is a strong risk factor for new-onset HFpEF[71] and is associated with worse NYHA classification, even after adjustments for eGFR.[72] Furthermore, it is an independent predictor of unfavorable outcome in patients admitted with HFpEF.[73] In chronic HFpEF, data are less compelling. In one study, there was a trend for predicting death or HF admission, but without significance in multivariate analysis.[12] Table 1 provides a summary on the role of important biomarkers in HFpEF.

Future Biomarkers

Circulating microRNAs (miRNAs)

They offer attractive potential as epigenetic disease biomarkers due to their biological stability and ready accessibility in liquid biopsies.[12] Numerous clinical cohort studies have revealed unique miRNA profiles in different disease settings, suggesting their utility as markers with diagnostic and prognostic applications. In one study, a panel of eight HFpEF-related miRNAs was reported as valuable in identifying HFpEF.[74] However, there is no consensus on which specific miRNA might better serve as a HFpEF biomarker. Further research is needed to understand their role in HFpEF (Figure 3).

Metabolomics

Patients with HFpEF have a specific metabolic profile as compared to those with HFrEF. In an exploratory study,[75]

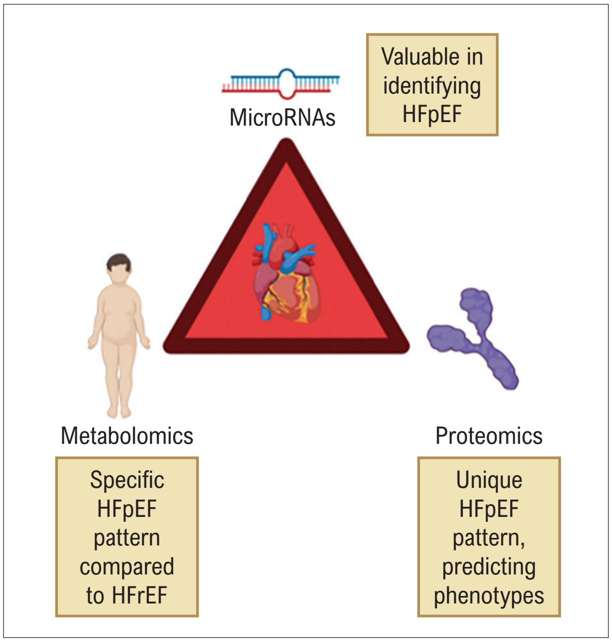

Figure 3 – *Novel biomarkers in HFpEF. The role of these new biomarkers in clinical practice still needs to be validated, but they may be useful in phenotyping HFpEF in the future. HFpEF: heart failure with preserved ejection fraction; HFrEF: heart failure with reduced ejection fraction.*

patients with new-onset HFpEF had a diverging metabolite pattern compared to that of patients with HFrEF, reflecting potential differences in pathophysiological mechanisms. Patients with HFpEF displayed elevated hydroxyproline, reflecting fibrosis; elevated symmetrical dimethylarginine, indicating oxidative stress; and elevated alanine, cystine, and kynurenine, reflecting a state of increased inflammation compared with patients with HFrEF. Patients with HFpEF also had lower levels of cGMP and cyclic adenosine monophosphate, suggesting impaired cell signaling. Finally, serine and arginine were lower in patients with HFpEF than in those with HFrEF, reflecting endothelial dysfunction.

Proteomics

An analysis of 92 proteins from the Olink Cardiovascular II Panel and their association with obese HFpEF has been recently reported in the LIFE-Heart study.[12] Obese patients with HFpEF exhibited higher circulating biomarkers of volume expansion (adrenomedullin), myocardial fibrosis (thrombospondin-2), and systemic inflammation (galectin-9, CD4) compared to obese non-HFpEF or lean HFpEF patients.

In the setting of HFpEF and diabetes, Hanff et al., using SomaScan assays and proteomic analyses of plasma from participants in the TOPCAT trial and the Penn Heart Failure Study, identified 10 proteins with differential expression in patients with HFpEF and diabetes. These proteins included fatty acid-binding protein, alpha-1-microglobulin/bikunin precursor, trafficking protein particle complex subunit 3, pigment epithelium-derived factor, tumor necrosis factor ligand superfamily member 15, ubiquitin-conjugating enzyme E2 G2, reticulon-4 receptor, insulin, cartilage intermediate layer protein 2, and apolipoprotein M. Of these, apolipoprotein M was found to mediate 72% of the association between diabetes and risk of cardiovascular death, aborted cardiac arrest, and HF hospitalization.[76] In addition, the use of SomaScan technology has shown that HFrEF, HFmrEF and HFpEF have unique patterns of circulating proteins.[77] Thus, it may be possible to use proteomic assays to more accurately predict the phenotype

Table 1 – Summary of the pathophysiology and potential role of different biomarkers in HFpEF

Biomarker	Mechanism of action	Role in HFpEF
Natriuretic peptides	Myocardial stretch; marker of hemodynamic load	Diagnosis and prognosis
hs-cTn	Released by cardiac ischemia or myocardial stress or injury	Predictor of mortality and incidence of HFpEF; adds prognostic value to NP
GDF-15	Inflammation, oxidative stress; secreted by cytokines	HF phenotyping; predictor of mortality; NT-proBNP/GDF-15 ratio differentiates HFpEF from HFrEF
ST2	High levels block the favorable effects of IL-33 by limiting activation of the cascade triggered by the IL-33/ST2L interaction	High levels associated with cardiac fibrosis and remodeling and worse outcomes
Galectin-3	Marker of inflammation, deposits type-1 collagen leading to fibrosis, inflammation, and cardiac remodeling	HFpEF phenotyping and risk stratification; predicts the development of HFpEF in patients with comorbidities
Inflammatory markers (TNF-α, IL1, IL6, IL8, and CRP)	Inflammation	Levels of TNF-α receptors are associated with the severity of diastolic dysfunction and symptoms;
FABP4	Development of obesity, insulin resistance, diabetes, and atherosclerosis	Predictor of death or heart failure admission
Cystatin C	Renal function marker; excess cystatin promotes myocardial fibrosis and hypertrophy	Strong risk factor for new-onset HFpEF; predicts outcomes, especially in acute HFpEF

CRP: C-reactive protein; FABP4: fatty-acid-binding protein 4; GDF-15: growth differentiation factor 15; HFpEF: heart failure with preserved ejection fraction; hs-cTn high-sensitivity cardiac troponin; IL: interleukin; NP: natriuretic peptides; NT-proBNP: N-terminal pro-B-type natriuretic peptide; ST2: suppression of tumorigenicity 2; TNF: tumor necrosis factor.

of patients with HF. Further research is needed to validate and translate proteomic data into clinical practice.

Conclusions

HFpEF is a complex disease whose pathophysiology is not completely understood. Biomarkers are useful tools in the management of HFpEF. NP are the gold standard biomarker for the diagnosis of HF in the whole spectrum of ejection fraction. However, their diagnostic performance in HFpEF is inferior to that observed in HFrEF, especially in obese patients.

For prognostic purposes, it seems reasonable that the use of multiple markers reflecting the activation of different pathophysiological pathways may more accurately identify high-risk individuals. NP and hs-cTn are useful cardiac prognostic markers and many non-cardiac biomarkers reflecting inflammation, fibrosis, and oxidative stress, among other pathways, may provide additional information.

The pathophysiological basis for identifying and classifying HFpEF based on a multimarker strategy seems logical and deserves further research. The information on non-cardiac components of HFpEF may increase our understanding of the disease and may be useful in determining HFpEF phenotypes that may guide therapy and clinical trials.

Author Contributions

Conception and design of the research, Acquisition of data and Writing of the manuscript: Villacorta H; Analysis and interpretation of the data: Villacorta H, Maisel AS; Critical revision of the manuscript for important intellectual content: Maisel AS.

Potential Conflict of Interest

Dr. Humberto Villacorta - Speaker honoraria from Roche Diagnostics

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Ethics approval and consent to participate

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

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