Role of cardiac biomarkers in heart failure with preserved ejection fraction

Mohamed Saad El-shetry, Ragab Abdelsalam Mahfouz, Mohamed Ibrahim Amin, Mohamed Arab, Mohammed Abdallah Omar Alteb, Mohamed Mesbah Taha
Cardiology Department, Faculty of Medicine, Zagazig University
Corresponding author: Mohammed Abdallah Omar Alteb
Email: altaebodi@gmail.com, Mobile: 01003559395

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Abstract:

Nearly half of all patients with heart failure have preserved ejection fraction (HFpEF) as opposed to reduced ejection fraction (HFrEF), yet associations of biomarkers with future heart failure subtype are incompletely understood.

Keywords: cardiac biomarkers, heart failure, preserved ejection fraction.

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Introduction:

Heart failure (HF) with preserved ejection fraction (HFpEF) is a heterogeneous disorder developing from multiple aetiologies with overlapping pathophysiological mechanisms. Circulating biomarkers reflect cardiac as well as non-cardiac abnormalities, and their measurements often provide insights into pathophysiological processes associated with HF ***(1)***

The clinical uptake of biomarkers for diagnosing HFpEF has generally been poor, with only cardiac natriuretic peptides (NPs) having emerged as clinically relevant. Indeed, current European Society of Cardiology (ESC)/Heart Failure Association guidelines provide a class IB recommendation for NPs for diagnosis of suspected HF and NPs are a major criterion for establishing the diagnosis of HFpEF ***(2)***

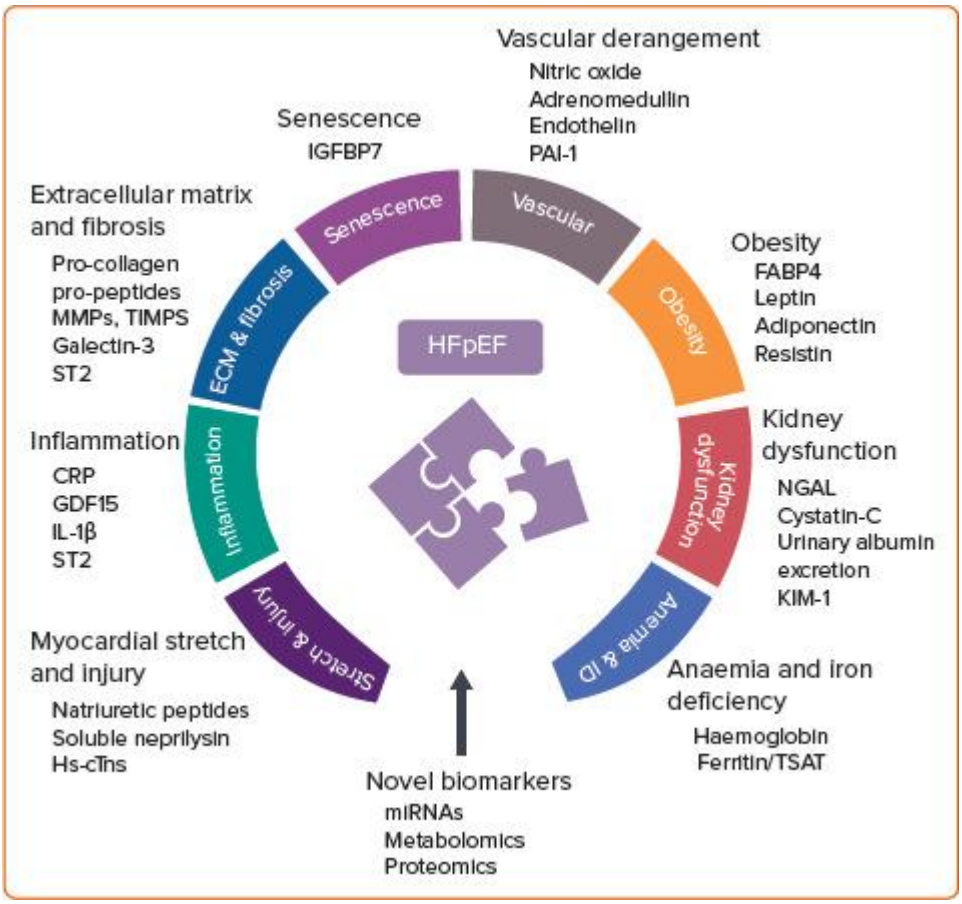

Figure (1): Holistic Schematic of Biomarkers in Heart Failure with Preserved Ejection Fraction ***(2)***

MYOCARDIAL STRETCH AND INJURY

a) Natriuretic Peptides

Three endogenous NPs are secreted as pre-prohormones: atrial natriuretic peptide (ANP), B-type natriuretic peptide (BNP) and C-type natriuretic peptide. All these peptides act as hormones with pleiotropic effects contributing to cardiovascular homeostasis and pressure and volume overload counter-regulatory mechanisms ***(3)***

BNP and N-terminal proBNP (NT-proBNP) exhibit longer plasma half-lives (22 minutes and 70 minutes, respectively) compared to ANP (2 minutes); most of the evidence related to NPs in HF is from these two NPs, which are the gold standard diagnostic and prognostic biomarkers in HF patients. The pathophysiological mechanism of NP elevation in the setting of HF is well understood: BNP is produced primarily and secreted in the cardiac ventricles as a pro-hormone in response to myocardial stretch, to later be cleaved into vasoactive BNP and inactive NT-proBNP. These NPs have been directly correlated with several haemodynamic measures including left

ventricular (LV) end-diastolic pressure, LV end-systolic and end-diastolic volumes and pulmonary capillary wedge pressure ***(4)***

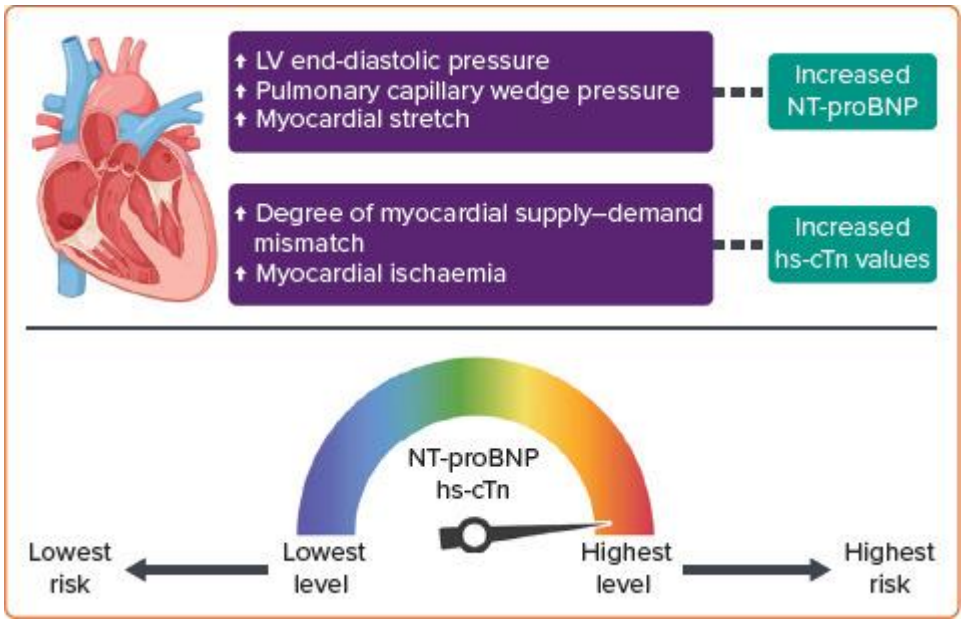

Figure (2): Biomarkers of Myocardial Stretch and Cardiac Injury in Heart Failure with Preserved Ejection Fraction ***(4)***

The utility of NPs in HFpEF is not restricted to their diagnostic capacity. Several studies have also investigated their ability to identify patients at risk for adverse events. A recent unsupervised cluster analysis based on a broad range of circulating biomarkers found that higher levels of NT-proBNP identify a subgroup of HFpEF patients (who also shared higher levels of cardiac troponin) who are at the highest risk of death and/or HF hospitalisation (62.8% over a median follow-up of 21 months) ***(5)***

In the acute setting, NT-proBNP level is also considered a strong independent predictor of all-cause mortality, as recently described in the study by Lopuszynski et al. performed in a cohort of patients with chronic HF exacerbation and HFpEF. In this respect, previous studies have also reported equal prognostic significance of either admission levels or discharge levels of NPs in patients with HFpEF hospitalised for acute decompensated HF. NPs also confer the same relative risk information in HFpEF as in HFrEF in this acute setting, with similar adjusted prognostic relative risks in patients with both phenotypes for the relative changes in NT-proBNP levels during hospitalisation ***(6)***

Finally, in the field of patient management, it has been suggested that measuring NP concentrations should be useful in guiding therapy in the whole spectrum of HF, including the

group of patients with HFpEF. However, current evidence does not support the routine measurement of BNP or NT-proBNP to guide titration of therapy ***(7)***

In this regard, the widespread strategy of using elevated plasma concentrations of NPs for patient selection in HFpEF trials has also been questioned, due to the lack of or lower benefit of irbesartan or aldosterone antagonists in patients with HFpEF and higher baseline NP values in the I-PRESERVE and TOPCAT trials, or the absence of sacubitril/valsartan treatment effect modification according to baseline NPs in the PARAGON-HF trial ***(8)***

b) Soluble Neprilysin

In the cardiovascular system, neprilysin cleaves numerous vasoactive peptides. Some of these peptides have vasodilating effects (including NPs, adrenomedullin and bradykinin), and others have vasoconstrictor effects (angiotensin I and II and endothelin [ET]-1, among others). Neprilysin serum levels (sNEP) exhibited significant prognostic value in both chronic and acutely decompensated HF. However, in patients with HFpEF results were controversial, perhaps due to different sNEP quantification methods ***(9)***

It is not only the prognostic role of sNEP that has been controversial: even blood sNEP concentrations can be very dissimilar with large differences among studies – some showing lower levels in HFpEF than in controls and others showing higher levels in HFpEF than in HFrEF patients. The correct quantification of sNEP remains a challenge that needs to be overcome to suppress potential biases regarding the interpretation of the different studies. Interestingly, some sNEP quantification methods showed that circulating sNEP was catalytically active ***(10)***

With the hypothesis that higher sNEP levels would correlate with lower NP levels, worse diastolic function, and subsequent clinical incident HFpEF, Reddy et al. performed a population study with 1,536 participants from Olmsted County, Minnesota. The authors found that low sNEP was paradoxically associated with worse diastolic dysfunction and hypertension but not with outcomes, including incident HF, over a median of 10.7 years of follow-up ***(11)***

Due to these controversial results the assessment of sNEP in HFpEF patients is not currently recommended. However, it has recently been speculated that higher sNEP levels may identify HFpEF patients who might benefit from treatment with sacubitril/valsartan ***(12)***

c) High-sensitivity Cardiac Troponin

High-sensitivity cardiac troponin (hs-cTn) is universally recognised for its central role in defining myocardial injury in patients with acute coronary syndrome. However, hs-cTn can also predict the development of HF and reflect ongoing myocardial injury in the wide spectrum of HF ***(13)***

More specifically, elevated hs-cTn discriminates a subgroup of patients with HFpEF who have ongoing myocardial damage, higher wall stress or impaired microcirculation, as evidenced

in a recent mechanistic study performed by Obokata et al. They assessed the relationship between troponin elevation and HFpEF physiology in 38 HFpEF patients and 20 control patients. HFpEF patients were found to have significantly higher troponin levels at rest, with the degree of elevation directly correlated to higher pulmonary capillary wedge pressure and worse systolic and diastolic tissue Doppler velocities. Troponin levels were also correlated with reductions in oxygen supply and a corresponding greater degree of supply–demand mismatch ***(14)***

Hs-cTn has been shown to be of value in predicting the onset of HFpEF over a very long period in high-risk subjects in the general population and the elderly. The role of hs-cTn as a predictive biomarker in chronic HFpEF has also been a matter of research ***(15)***

Several studies have identified a significant association between elevated hs-TnT at admission and at discharge with adverse events in patients hospitalised with decompensated HFpEF ***(16)***

The predictive capabilities of hs-cTnT and hs-cTnI for secondary events in HFpEF have also been assessed. Both hs-cTnT and hs-cTnI are elevated in chronic HFpEF and are independently associated with poorer outcomes in men (HR 3.33; 95% CI [1.82–6.09]) than in women (HR 1.35; 95% [CI 0.94–1.93]) ***(17)***

The predictive performance for composite outcomes was better for both hs-cTn assays in HFpEF than in HFrEF, but the strongest performance in HFpEF appeared to be from hs-TnT. The prognostic role for hs-cTn assays in HFpEF also has a sex-specific concern, as the more sensitive hs-cTnI assay appears to be a better predictor of outcome in men than in women ***(18)***

When combining the mechanistic data with the described associations of hs-cTn with adverse clinical outcomes, it appears reasonable to proclaim hs-cTn as a surrogate for a clinically meaningful HFpEF endpoint. This issue was partially addressed in the PARAGON-HF trial. The investigators found not only that hs-TnT was reduced by sacubitril/valsartan therapy compared with valsartan, but also that patients with a decrease in hs-TnT from randomisation to 16 weeks to a value to at or below the median value of 17 ng/l subsequently had lower risk of the composite outcome compared with those who had persistently elevated hs-TnT values. Further research will be required to determine whether therapies targeting the mechanism of hs-cTn elevation can improve symptom burden and clinical outcomes in the HFpEF population ***(19)***

INFLAMMATION

a) C-reactive Protein

C-reactive protein (CRP) may activate the complement system and stimulate cytokine production and thereby cause myocyte loss and promote LV remodelling and dysfunction. CRP has been shown to attenuate nitric oxide (NO) production and has a direct proinflammatory effect on human endothelial cells. Thus, CRP might worsen HF through multiple mechanisms. There is

a close relationship between the number of comorbidities and plasma CRP level. Serum levels of CRP and pentraxin (PTX)-3, an acute phase protein of the PTX superfamily that also includes CRP, were both found to be significantly higher in HFpEF patients when compared with the non-HF reference group. PTX-3 was found to be an independent inflammatory marker correlated with the presence of LV diastolic dysfunction and HFpEF ***(20)***

b) Interleukin-1β

Interleukin (IL)-1β is a member of the IL 1 family of cytokines. This cytokine is produced by activated macrophages as a proprotein which is proteolytically processed to its active form by caspase 1 (CASP1/interleukin-1-converting enzyme). This cytokine is an important mediator of the inflammatory response and is involved in a variety of cellular activities, including cell proliferation, differentiation and apoptosis. Preclinical data show that the IL-1 family of cytokines contributes to cardiac dysfunction, and IL-1 blockade with anakinra (a recombinant IL-1 receptor antagonist) in patients with HF may improve cardiorespiratory fitness and prevent HF hospitalisations ***(21)***

c) Interleukin 1 Receptor-like-1

Interleukin-1 receptor-like 1, also known as suppression of tumorigenicity 2 (ST2) has multiple isoforms, including a transmembrane form (ST2 ligand; ST2L) and a soluble circulating form (soluble ST2; sST2). Both ST2L and sST2 are expressed by cardiomyocytes and cardiac fibroblasts in response to mechanical stress, and both isoforms bind to IL-33. IL-33 is also induced by cellular stretch and apparently protects against fibrosis and hypertrophy in mechanically strained tissues via activation of myeloid differentiation primary response gene 88, interleukin-1 receptor-associated kinase, extracellular signal-regulated kinase and, ultimately, nuclear factor-κB ***(22)***

d) Growth Differentiation Factor 15

Growth differentiation factor 15 (GDF15) is a member of the transforming growth factor β cytokine superfamily that is highly expressed in states of inflammatory stress. GDF15 integrates information from cardiac and extracardiac disease pathways that are linked to the incidence, progression and prognosis of HF. Increased circulating levels of GDF15 are associated with an increased risk of developing HF in apparently healthy individuals. After an acute coronary syndrome, elevated levels of GDF15 are indicative of an increased risk of developing adverse LV remodelling and HF. In patients with established HF, the levels of GDF15 and increases in GDF15 over time are associated with adverse outcomes. The information provided by GDF15 is independent of established risk factors and cardiac biomarkers, including BNP ***(23)***

EXTRACELLULAR MATRIX AND FIBROSIS

a) Pro-collagen Propeptides

One of the hallmarks of interstitial fibrosis is deposition of types I and III fibrillar collagen. The collagen precursor, pro-collagen, consists of three polypeptide chains arranged in a triple helix, with non-helical N-terminal and C-terminal sequences. The N-terminal and C-terminal peptides are cleaved by endopeptidases after pro-collagen has been secreted from the cell. Elevated levels of pro-collagen type III N-terminal peptide (PIIINP) have been observed in individuals with hypertension, dilated cardiomyopathy, hypertrophic cardiomyopathy and recent MI, suggesting that the circulating peptide may be a useful marker of active myocardial collagen synthesis ***(24)***

b) Matrix Metalloproteases and Tissue Inhibitor of Metalloproteinase

Matrix metalloproteases (MMPs) are calcium-dependent zinc-containing endopeptidases. These enzymes are capable of degrading all kinds of extracellular matrix proteins, but can also process a number of bioactive molecules. They are known to be involved in the cleavage of cell surface receptors, the release of apoptotic ligands (such as Fas ligand) and chemokine/cytokine inactivation. MMPs are also thought to play a major role in cell behaviours such as cell proliferation, migration, differentiation, angiogenesis, apoptosis and host defense. Tissue inhibitor of metalloproteinase (TIMP) is a natural glycoprotein inhibitor of the MMPs. MMP2 and MMP9 activity and TIMP1 protein levels were enhanced in haemodynamic models of HFpEF, while metabolic models showed no changes in MMP2, -8, -9, -11, -14, -15, TIMP-1, -2 and -3 mRNA expression ***(25)***

c) Galectin-3

Galectin-3 is a β-galactoside-binding member of the lectin family and is encoded by a single gene, *LGALSS3*, located on chromosome 14. Galectin-3 is an ~30 kDa protein and contains a carbohydrate recognition binding domain of ~130 amino acids that enables the specific binding of β-galactosidases. Galectin-3 has been linked to HF development and is implicated in a variety of processes that are thought to play an important role in the pathophysiology of HFpEF, such as myofibroblast proliferation, fibrogenesis, tissue repair, inflammation and ventricular remodelling ***(26)***

VASCULAR MECHANISMS

a) Nitric Oxide

NO is produced by the enzymatic action of NO synthase (NOS) in vascular endothelium. Vascular actions of NO include direct vasodilation, indirect vasodilation by inhibiting vasoconstrictor influences, along with anti-thrombotic, anti-inflammatory and anti-proliferative effects. Low myocardial cyclic guanosine monophosphate (cGMP)-dependent protein kinase type I (PKG) activity is associated with raised cardiomyocyte resting tension and increased myocardial nitrosative/oxidative stress in HFpEF patients compared with HFrEF patients and patients with aortic stenosis ***(27)***

b) Adrenomedullin

Adrenomedullin (ADM) is a potent vasodilator peptide, with additional immunomodulating, antiproliferative and antiapoptotic effects. ADM gene expression is significantly increased in the Dahl salt-sensitive rat model of HFpEF ***(28)***

c) Endothelin

ET is the most potent vasoconstrictor peptide known in humans. It is produced in higher concentrations by endothelial cells and is involved in the regulation of vascular tone ***(29)***

d) Plasminogen Activator Inhibitor-1

Plasminogen activator inhibitor-1 (PAI-1) is a serine protease inhibitor that functions as the principal inhibitor of tissue plasminogen activator and urokinase, the activators of plasminogen and hence fibrinolysis. Thus, elevated PAI-1 is a risk factor for thrombosis and atherosclerosis. Accordingly, PAI-1 levels were increased in patients with HFpEF in comparison with healthy controls, as were D-dimer and tissue plasminogen activator levels, suggesting that HFpEF is associated with a procoagulant state ***(30)***

SENESCENCE

a) Insulin-like Growth Factor-binding Protein 7

The major function of insulin-like growth factor-binding protein (IGFBP) 7 is to regulate the availability of insulin-like growth factors. It also stimulates cell adhesion and is associated with inflammation, cellular senescence, tissue aging and obesity. Some proteins involved in inflammation, such IGFBP7, formed a conserved network in HFpEF across two independent cohorts from the PROMIS-HFpEF study and may mediate the association between comorbidity burden and echocardiographic indicators of worse haemodynamics and RV dysfunction ***(31)***

Patients with a pan-inflammatory phenotype exhibited the highest circulating levels of inflammatory mediators, more comorbidity, more HF hospitalisations, higher left-atrial volume index and NT-proBNP level, worse renal function, the highest levels of fibrotic biomarkers such IGFBP7 and the lowest functional capacity, in an HFpEF study that used unsupervised machine learning. Nevertheless, higher concentrations of IGFBP7 were associated with increased risk of cardiovascular events in patients from the I-PRESERVE trial, but after multivariable adjustment this association was no longer present ***(32)***

NOVEL BIOMARKERS

a) Circulating microRNAs

Circulating microRNAs (miRNAs) offer attractive potential as epigenetic disease biomarkers by virtue of their biological stability and ready accessibility in liquid biopsies.

Numerous clinical cohort studies have revealed unique miRNA profiles in different disease settings, suggesting their utility as markers with diagnostic and prognostic applications ***(33)***

The discovery of microRNA clusters that are differentially expressed in HFrEF and HFpEF patients provides an approach to delineate the different pathobiological pathways underlying HFrEF and HFpEF. A putative biological pathway affected by a panel of eight HFpEF-related miRNAs (hsa-miR-193a-5p, hsa-miR-30a-5p, hsa-miR-106a-5p, hsa-miR-191-5p, hsa-miR-486-5p, hsa-miR-181a-2-3p, hsa-miR-660-5p and hsa-miR-199b-5p) has been reported as valuable in identifying HFpEF ***(34)***

However, there is no consensus on the choice of specific circulating miRNAs that might better serve as HFpEF biomarkers. A recent report found circulating miR-181c as a marker of the response to exercise training in patients with HFpEF. Further research is needed to understand their added value in diagnosis and prognosis at the clinic, beyond their research interest ***(35)***

b) Metabolomics

Patients with new-onset HFpEF compared with patients with new-onset HFrEF display a different metabolic profile associated with comorbidities such as diabetes and kidney dysfunction. In an exploratory study, new-onset HFpEF patients had a diverging metabolite pattern compared with that of HFrEF patients, reflecting potential differences in pathophysiological mechanisms. First, HFpEF patients 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 HFrEF patients. Second, HFpEF patients had lower levels of cGMP and cyclic adenosine monophosphate, suggesting impaired cell signalling; lower L-carnitine, indicating mitochondrial dysfunction; and lower levels of lysoPC (18:2) associated with impaired lipid metabolism. Third, serine and arginine levels were lower in HFpEF than in HFrEF, reflecting endothelial dysfunction in HFpEF ***(36)***

c) Proteomics

Exploration of 92 proteins from the Olink cardiovascular II panel and their association with obese HFpEF has been recently reported in the LIFE-Heart study (999 patients with HFpEF and 999 patients without HF). Obese HFpEF patients 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 ***(37)***

The use of SomaScan technology showed that patients with HFrEF, HF with mid-range ejection fraction (HFmrEF), and HFpEF had unique variations in circulating proteins which reflected distinct biological pathophysiologies. Bioinformatics analysis revealed biological themes that were unique to HFrEF, HFpEF and HFmrEF patients, suggesting that it may be possible to use proteomics assays to more accurately predict clinical phenotypes of HF patients. Further research is needed to validate these results and translate the proteomic data to the bedside ***(38).***

The use of machine-learning algorithms applied to a wide range of biomarkers in HFpEF cohorts has identified several clusters a with different cardiovascular phenotypes and outcomes ***(39).***

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