

Review Article

Predicting Heart Failure Phenotypes using Cardiac Biomarkers: Hype and Hope

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Early risk stratification in heart failure (HF) might improve clinical outcomes via providing individualized treatment care. In this context, measuring plasma levels of cardiac biomarkers, i.e. natriuretic peptides, cardiac specific troponins, metabolomic intermediates, galectin-3, ST2, cardiotrophin-1, soluble endoglin, growth differentiation factor 15, microRNAs merges attractively. By now, the role of cardiac biomarker in prediction of early stage of HF with preserved ejection fraction (HFpEF) and HF with reduced ejection fraction (HFrEF) is not still fully understood. This review explores our current knowledge on the utility of cardiac biomarkers for reclassification of patients with different HF phenotypes. It has been reported that several biomarkers reflected the differentiation of fibroblasts into myofibroblasts that subsequently alter collagen turnover, cardiac fibrosis and inflammation; and might have diagnostic and predictive value in HFpEF and HFrEF. The best candidate biomarkers for detecting early stage HF were ST2, galectin-3, CT-1, and GDF-15. However, increased plasma concentration of these biomarkers was not specific for the HFpEF and HFrEF patient populations. Finally, more investigation is required to validate early diagnostic and prognostic value of novel biomarkers in HFpEF and HFrEF.

Keywords: Heart failure phenotypes; Biomarkers; Prognostication; Risk stratification**Abbreviations**

BNP: Brain Natriuretic Peptide; CAD: Coronary Artery Disease; CABG: Coronary Artery Bypass Grafting; GDF: Growth Differentiation Factor; CT-1: Cardiotrophin-1; CV: Cardio Vascular; HF: Heart Failure; HFpEF: Heart Failure with Preserved Ejection Fraction; HFrEF: Heart Failure with Reduced Ejection Fraction; LV: Left Ventricle; mr-ANP: Mig-regional Atrial Natriuretic Peptide; PCI: Percutaneous Coronary Angioplasty Procedure; sST2: Soluble ST2

Introduction

Heart failure (HF) remains an important clinical entity that leads to an increase in prevalence worldwide due to improved survival after HF diagnosis [1,2]. Recent studies have shown sufficient differences in the etiology, pathophysiology, clinical presentation and outcomes, as well as prognosis between HF with preserved ejection fraction (HFpEF) and HF with reduced ejection fraction (HFrEF) [3-5].

HFpEF is a phenotypic heterogeneous clinical syndrome characterized by cardiovascular (CV) disease, dysmetabolic and inflammatory states associated with advanced age and various non CV co-morbidities that finally lead to impairment of myocardial structure and function [6,7]. Although EF >50% is currently used as the definition of HFpEF, this cutoff point is widely debated, as probably inadequate criterion [8,9]. However, in fact that older age, female gender, diabetes mellitus, hypertension, atrial fibrillation, and chronic kidney disease are strong predictors of HFpEF development [10-12]. Based on evidence from endomyocardial biopsies, some of the specific cardiac structural phenotypes to be targeted in HFpEF may be represented by myocyte hypertrophy, interstitial

fibrosis [13,14]. HFrEF has been described as a disease of mean aged-elderly subjects with male predominance. Therefore, dilation cardiomyopathy, ischemic, inflammatory, diabetic etiology, rarely with arterial and pulmonary hypertension frequently associates with HFrEF development [15,16]. Cell loss due to ischemia, apoptosis and necrosis, myocardial inflammation related to oxidative stress, expanded interstitial fibrosis led to disintegrity of cardiac wall, increased passive myocardial stiffness, worsening of cardiac configuration and contractile function is common for HFrEF [17].

Many questions remain unanswered regarding differences in the molecular signals that initiate development of HFpEF and HFrEF [18]. In this context, it could be possible to appropriately stratify HFpEF and HFrEF patients at risk using biomarkers. Recently, several cardiac biomarkers, i.e. brain natriuretic peptides, cardiac specific troponins, metabolomic intermediates, galectin-3, ST2, cardiotrophin-1, soluble endoglin, growth differentiation factor 15, and other molecules, have widely investigated (Table 1). However, the current data on the interrelationship of these biomarkers and phenotypes of HF are sufficiently limited. The aim of the review is devoted to accumulation of knowledge regarding utility of cardiac biomarkers aimed reclassification of patients with different phenotypes of HF.

Brain Natriuretic Peptides

Within last two decades cardiac natriuretic peptides (BNP and NT-proBNP) are defined biomarkers that may use to screen for LV systolic dysfunction in patients with symptoms suggestive of HF. By now BNP and NT-proBNP are now included in the current guidelines for HF diagnosis, management and risk assessment because of their

Table 1: Comparison of the diagnostic and prognostic abilities of the different HF biomarkers.

Biomarker	Source of production	Inductor of release	Relation to pathophysiological features	Clinical implication
Natriuretic peptides	Cardiac myocytes	Stretching cardiac wall, cell injury and necrosis	Biomechanical stress	Predictors of cardiac dysfunction, HF manifestation, HF-related mortality, CV death and hospital admission
High-sensitive cardiac troponins	Cardiac myocytes	Cell injury and necrosis	Injury biomarker	Predictors of HF manifestation in asymptomatic subjects, the risk stratifier of fatal CV events, clinical HF-related outcomes, and primary / re-admissions in HF patients
Galectin-3	Cardiac myocytes, activated macrophages / mononuclears, fibroblasts	Low-grade inflammation response, neuro-endocrine activation	Inflammation and fibrosis	Predictor of cardiac remodeling, fibrosis, onset of HF in general population, surrogate marker of a worse prognosis, mortality and re-admission in HF
Soluble ST2	Cardiac myocytes and fibroblasts	Mechanical strain of cardiac wall	Inflammation and biochemical stress	Predictor of CV death, progression of HF and prognosis in HF patients beyond other CV risk factors
Cardiotrophin-1	Immune cells	Low-grade inflammation response	Inflammation, growth and differentiation of cells	Predictor of cardiac and vascular remodelling, HF development and progression
Endoglin	Cardiac myocytes, activated macrophages / mononuclears, fibroblasts, endothelial cells, immune cells.	Low-grade inflammation response, neuro-endocrine activation	Promoter of inflammation, endothelial dysfunction, cardiac fibrosis, and vascular remodeling	Predictor of CV events, atherosclerosis and HF
GDF-15	Cardiac myocytes, activated macrophages / mononuclears, fibroblasts, myofibroblasts, endothelial cells, immune cells	Biochemical stress	Promoter of inflammation, cell growth and differentiation	Predictor of HF manifestation and development, CV and HF-related death and clinical outcomes
Reactive oxidative species	All cell types	Cell injury / necrosis / activation	Injury biomarker	Predictor of HF progression, HF-related death and outcomes
microRNA	All cell types	Activation and apoptosis of cells	Growth and differentiation of cell, immunity, proliferation, inflammation	Not clear, probably signature miRNAs might distinguish between HFrEF and HFpEF

Abbreviations: CV: cardiovascular; HF: Heart Failure; GDF-15: Growth Differentiation Factor 15.

high specificity and sensibility [19]. NT-proBNP > 240 pg/mL predicts symptomatic HF with optimal sensitivity (96%) and specificity (79%) [20]. However, sensitivity, specificity and diagnostic accuracy of BNP and NT-proBNP are closely related to pre-specified cutoff points (Table 2) [20].

Despite BNP and NT-proBNP improve discrimination modestly for HF above and beyond conventional risk factors and substantially improve risk classification for HF, peak concentrations of BNP and NT-proBNP and serial measurements of NT-proBNP levels in longitude are not able to allow differencing HF phenotypes [21,22]. However, there were important differences in the prognostic value of NT-proBNP in HFpEF versus HFrEF in the NT-proBNP-guided arm of TIME-CHF study [23]. Indeed, patients with HFpEF and HFrEF have variations in their BNP and weight before decompensation [24]. Moreover, NT-proBNP has demonstrated less prognostic value in HFpEF compared to HFrEF, but has not been predicted a development of HFpEF or HFrEF. It has been suggested that the clinical examination, along with BNP, with optimal sensitivity (92%) and specificity (91%) may facilitate early detection of early stage HFrEF and allow implementation of interventions aimed at preventing progression to symptomatic HFrEF [25]. Obviously, NT-proBNP lost significance as a risk stratifier in ambulatory patients with stable HF and probably in those who have HFpEF. There are attempts to mig-regional atrial natriuretic peptide (mr-ANP) and NT-proANP to screen HFpEF and HFrEF in individuals, when diagnosis of HF is not obvious. In this setting diagnostic value and prognostic ability for HF-related mortality and CV hospitalization for both mr-ANP and NT-proANP were not superior that NT-proBNP [26].

Cardiac Troponins

Recent studies have shown that elevated level of high-sensitive cardiac troponin I (hs-cTnI) and T (hs-cTnT) as biomarkers of subclinical myocardial injury may provide clinically useful prognostic information both concerning the future risk of HF manifestation in asymptomatic subjects and the risk of fatal events and primary / re-admissions in the hospital in those with already established symptomatic acute, acutely decompensated, and chronic stable HF related to ischemic and non-ischemic causes [27-30]. Moreover, cardiac troponin mutations are considered a cause of impaired relaxation in the mutant cardiac myocytes due to myofibril hypersensitivity to Ca²⁺ [31].

Because cardiac specific troponins exhibited the strongest associations with hospitalization, survival and outcomes in HF, there are expectations regarding an ability of troponins emerge etiology-dependent relation with phenotypes of HF. Seliger et al. [32] hypothesized that hs-cTnT would differentiate HF risk among older adults with left ventricular hypertrophy (LVH). In Cardiovascular Health Study authors found that the adjusted risk of HFrEF was 7.8 times higher among those with the highest tertile of hs-cTnT and LVH (HR=7.83; 95% CI: 4.43 - 13.83). Interesting that patients with LVH and longitudinal increases in hs-cTnT or NT-proBNP were approximately three-fold more likely to HF development, primarily HFrEF, compared with those without LVH and with stable biomarkers. Thus, in this study authors were not able to find sufficient advantages regarding hs-cTnT compared NT-proBNP to characterize sub-phenotypes of HF. In another study Neeland et al [33] reported that identifying a malignant sub-phenotype of LVH was the better

Table 2: Sensitivity, specificity and diagnostic accuracy of natriuretic peptides to detecting HFpEF and HFrEF.

BNP levels, pg/mL	Sensitivity, %	Specificity, %	Accuracy, %
105	86	94	89
195	94	85	90
240	96	79	89

predictive surrogate marker then low-elevated level of hs-cTnT and even increased NT-proBNP among asymptomatic individuals with high risk for progression to HF and CV death in generally population. Therefore, there was evidence regarding data about that the higher levels of cTnT and NT-proBNP were correlated well with the risk of HF in older adults, but did not associated with phenotypes of HF [34]. Overall, circulating level of cell injury biomarker is not powerful tool for HF phenotype detection.

Systematic Metabolomic Biomarkers

Zordoky et al [35] suggested that a systematic metabolomic analysis would reveal a novel metabolomic fingerprint of HFpEF that will help understand its pathophysiology and assist in establishing new biomarkers for its diagnosis. Indeed, compared to non-HF control, HFpEF patients demonstrated higher serum concentrations of acylcarnitines, carnitine, creatinine, betaine, and amino acids; and lower levels of phosphatidylcholines, lysophosphatidylcholines, and sphingomyelins. Medium and long-chain acylcarnitines and ketone bodies were higher in HFpEF than HFrEF patients. Authors predisposed that this mentioned above metabolomic fingerprint has been utilized to identify two novel panels of metabolites that can separate HFpEF patients from both non-HF controls and HFrEF patients. However, this assumption requires more investigations.

Galectin-3

It has been suggested that various alternative biomarkers might give insight into the different pathways of HF pathophysiology, and they probably could help to identify generally population individuals at higher risk of HF developing and HF patients with poor outcomes [36]. Galectin-3 is a soluble beta galactoside-binding lectin produced by activated macrophages which binds and activates the fibroblasts [37]. Galectin-3 is considered a biomarker that mediates an important link between inflammation and fibrosis, which play a pivotal role in CV remodeling. Indeed, it has an established the pathogenetic role of Galectin-3 in the several setting of pressure overload, neuro-endocrine activation, hypertension, coronary artery disease/myocardial infarction, atrial fibrillation, and HF.

Galectin-3 has emerged a predictive value for the onset of HF in apparently healthy patients and has been found being surrogate marker of a worse prognosis, mortality and re-admission in HF [38,39]. However, serial measurements of galectin-3 level in ambulatory HF patients might not be of benefit [40].

In context of determining of different phenotypes of HF, measurement of circulating Galctin-3 might have a significant value because elevated level of Galectin-3 was found in patients with impaired LV diastolic function, but without symptomatic HF [41]. Gurel et al [42] reported that Galectin-3 could be a promising biomarker for the detection of LV diastolic dysfunction in patients

undergoing maintenance hemodialysis. It has been suggested that this biomarker could be useful surrogate of structural and functional abnormality of the myocardium among individuals at higher risk of HFpEF development especially associated with hypertension, coronary artery disease and diabetes [43,44]. However, there are not irresistible evidences regarding being of clinically significant advantages of Galectin-3 in prediction of HFpEF evolution compared with HFrEF development.

ST2

Soluble ST2 (sST2), a peptide belonging to the interleukin-1 receptor family, is secreted cardiomyocytes and cardiac fibroblasts under mechanical strain and thus it is concerned a biomarker of myocardial fibrosis, cardiac stretch and CV remodeling [45,46]. Measurement of sST2 is useful for risk stratification of death and prognosis prediction in HF patients beyond other CV risk factors [47]. Indeed, the sST2 concentration showed a weak correlation with the NYHA functional class, LFEF, other cardiac performances, and renal function [48,49]. Recent studies have shown that sST2 may have a special superiority as a risk predictor in HFpEF and HFrEF compared with natriuretic peptides and Galectin-3 [50,51]. However, there are not current data on the predictive value of sST2 concentration for HFpEF or HFrEF development.

Cardiotrophin-1

Cardiotrophin-1 (CT-1) is a member of the interleukin 6 cytokine superfamily and one of the endogenous ligands for gp130 signaling pathways in the heart with controversial biological effect. Indeed, CT-1 is able to induce hypertrophic growth and contractile dysfunction in cardiomyocytes, as well as it has potent hypertrophic and survival effects on cardiac myocytes [52]. CT-1 is closely associated with many CV diseases, i.e. hypertension, myocardial infarction, and HF, and exhibits a cardio protective effect in ischemia-reperfusion injury during GABG and angioplasty [53]. Recent clinical studies have shown that CT-1 level is increased in HF patients and is significantly correlated with the LV mass index, suggesting that CT-1 plays an important role in structural LV remodeling [54,55]. Interestingly, increased CT-1 plasma level might predict inappropriate LV mass merge in hypertensive subjects [56] and development and progression of HF [57]. Moreover, CT-1 is elevated in patients with HFpEF and is associated with NT-proBNP and estimated LV filling pressures [58]. Whether increased serum CT-1 may provide additional information to risk stratification in development of HFrEF or HFpEF is not completely clear.

Soluble Endoglin

Endoglin (also known as CD105) is a membrane co-receptor for transforming growth factor- β , which is released into the circulation as soluble form, which disrupts TGF β 1 signaling in endothelium and thereby promotes inflammation, endothelial dysfunction, cardiac fibrosis, and vascular remodeling [59,60]. Indeed, soluble endoglin is required for vascular barrier function, endothelial survival and homeostasis of the adult microvasculature, although this molecule is expressed in cardiac fibroblasts and may modulate profibrogenic actions of angiotensin II [61].

Recent clinical studies have revealed that the expression of

endoglin is increased in patients with atherosclerosis and that soluble endoglin level is thought to predict CV events in patients with chronic coronary artery disease after PCI [62]. There are evidences regarding the predictive role of elevated serum endoglin in patients with pre-eclampsia and [63]. In patients with HFrEF elevated soluble endoglin predicted elevated LV end-diastolic pressures, and well correlated with New York Heart Association class, irrespective of the LVEF, as well as with both atrial and brain natriuretic peptides [59,64]. The ability of soluble endoglin in prediction of HFpEF and HFrEF is not understood, while there are expectations regarding the role of this biomarker for prognostication of LV dysfunction at early onset. However, extended scrutinizes are required to be receive more information for assay of this assumption.

Growth Differentiation Factor 15

Growth differentiation factor 15 (GDF-15) is a stress-responsive cytokine, which belongs to super family of the transforming growth factor beta [65]. GDF-15 is widely presented in the wide spectrum various cells and plays a pivotal role in inflammation, cell growth and differentiation. Elevated GDF-15 was found in patients with established CV diseases (hypertension, stable coronary artery disease, acute coronary syndrome, myocardial infarction, ischemic and none ischemic-induced cardiomyopathies, HF, atrial fibrillation), type two diabetes mellitus, chronic renal disease, infection, liver cirrhosis, and malignancy [66].

Recent studies have revealed that GDF-15 was associated with NYHA class, NT-proBNP and exercise capacity, suggesting the marker has diagnostic and potential prognostic value in HF [67-69]. It has been suggested GDF-15 might categorize HFrEF and predict major HF-related clinical outcomes [70]. Chan et al [71] have reported that plasma levels of GDF15 in HFpEF and HFrEF were similar. Therefore, there was an independent prognostic utility of GDF15 in HFrEF and HFrEF. Indeed, authors have shown that GDF15 was a significant independent predictor for composite outcome even after adjusting for important clinical predictors including hsTnT and NT-proBNP. Overall, GDF15 was not able to help to detect the early stage of HFpEF, and this biomarker has been produced a very limited evidence regarding determination of diastolic dysfunction.

Oxidative Stress Markers

Recent animal studies have suggested a role of renin-angiotensin system (RAS) activation and subsequent cardiac oxidation in HFpEF [72]. It has been postulated that free reactive oxidative species (ROS) are required to generate cardiac RAS activation and further progressive cardiac remodeling [73]. However, the role of ROS in HFpEF development is still nor fully understood. In clinical study Hirata et al [74] have reported that ROS were associated with the severity of HF and predicted future CV events in HFpEF. In contrast, Negi et al [75] have reported that oxidative stress markers, i.e. derivatives of reactive oxidative metabolites, F2-isoprostanes, and ratios of oxidized to reduced glutathione and cysteine, were not associated with HFpEF development and progression. Overall, ROS production might not relate to HF phenotype directly. It has been suggested that beneficial long-term effects of interference with the RAS may be related to reduction of oxidative stress within the cardiac wall, mediated in part by co-morbidities coexisting HF.

MicroRNA Markers

MicroRNAs (miRNAs) are endogenous not coding RNAs with short strands of approximately 21-25 nucleotides, which are emerging as important biomarker candidates for various CV diseases, including HF [76]. Emerging evidence shows that miRNAs exert their regulatory effects by directly binding to the 3'- untranslated regions of their target genes. Theoretically, there is possibility to identifying miRNAs that are specific to HFrEF and HFpEF. In fact, altered levels of miR-125a-5p, -183-3p, -193b-3p, -211-5p, -494, -638, and -671-5p were found in HFrEF patients, and levels of miR-1233, -183-3p, -190a, -193b-3p, -193b-5p, and -545-5p were distinguished HFpEF from non-HF persons [77]. Authors reported that only miR-125a-5p, -190a, -550a-5p, and -638 have distinguished HFrEF from HFpEF. Ellis et al [78] have shown that miR-103, miR-142-3p, miR-30b, and miR-342-3p, were differentially expressed between HF and non-HF subjects, and distinguished between HFrEF and HFpEF in screening. The main limitations that sufficiently limit clinical implementation of detecting of miRNA signature are lack of strong biological correlation between circulatory miRNA levels and the relevant organ/tissue expression in HF. The next limitation regarding distinguished levels of miRNAs between HFrEF and HFpEF persons is the fact that individually circulating NT-proBNP level was far superior in predicting HF compared with signature miRNAs. On the other hand, combining microRNA levels with NT-proBNP might add diagnostic value to differentiate HFrEF and HFpEF.

Conclusion

In conclusion, several reports have shown that biomarkers reflected the differentiation of fibroblasts into myofibroblasts, subsequently alter collagen turnover, cardiac fibrosis, and inflammation might have diagnostic and predictive value in HFpEF and HFrEF. The best candidates for determining of early stage of HF development were sST2, galectin-3, CT-1, and GDF-15. However, increased plasma concentrations of these biomarkers were not specific for a distinct disease group of HFpEF and HFrEF. Finally, more investigations are required to point the role of novel biomarkers in prediction of HF and determination of early stage of the HFpEF and HFrEF development. It has needed to emphasize in particular, apart from well investigated sST2, galectin-3, CT-1, and GDF-15, new biomarkers, i.e. signature of miRNAs, for clinical use and reclassification would be always welcome.

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