Chapter 12

Biomarkers and Heart Failure

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Abstract

Heart failure (HF) represents fatal endpoint of all cardiovascular diseases. Acute and chronic HF is a complex, heterogeneous syndrome consisting of many overlapping syndromes making its diagnosis and treatment more challenging. There is no single test for diagnosis of HF, and diagnosis is based on clinical judgment driven by a combination of history, physical examination, and appropriate tests. Despite improvements in clinical management within the last 50 years, it has still been a disease of poor prognosis. Attempts to further improve its prognosis can only be achieved by understanding pathophysiology of HF clearly and finding, developing, and using appropriate and new clinical biochemical markers for diagnosis of each different clinical subtype and hence unique intervention of that specific subtype of HF. This review is an overview of biomarkers, which are either currently used in the clinical practice or hold promise for future use in patients with both chronic and acute HF.

Keywords: heart failure, diagnosis, prognosis, biochemical markers

1. Introduction

Heart failure (HF) is the end stage of all the cardiovascular diseases. It is an important mortality and morbidity cause. It is a syndrome that can be defined clinically by a collection of symptoms (dyspnea, fatigue, and exertional intolerance) and signs (edema, rales, and gallop) that are caused by a cardiac disorder [1]. In half of the patients with HF, inadequate pumping action of the heart is the main cardiac disorder forming the HF with reduced ejection fraction (HFrEF). In the other half, abnormality in the relaxation properties of the heart is the main cardiac disorder forming the HF with preserved ejection fraction (HFpEF). HFrEF and HFpEF share the same clinical phenotype. First of all, HF is a clinical diagnosis. Unfortunately, diagnosis of HF is not an easy task and cannot be made only by clinics because symptoms and signs of HF are nonspecific.

Rather, the diagnosis is based on clinical judgment using history, physical examination, and combination of appropriate tests. Biomarkers form complementary information in addition to the clinics and the other tests used, help for the diagnosis, prognosis, and follow-up of the HF patients, and sometimes form the basis for implementing specific treatment.

2. Biomarkers

The definition of biomarker is as follows: biomarkers are parameters which can be measured objectively and assessed as an indicator of normal biologic or pathogenic process or response to treatment. An ideal biomarker should have the capability of reflecting the pathway centrally important to the disease under investigation, thereby providing therapeutic insights. An ideal biomarker should have three important characteristics: (1) It should be measured in a short time with low cost. (2) It should add complementary information to clinical evaluation. (3) It should aid to the treatment of HF. Biomarkers with these characteristics can be used for confirming the presence or absence of HF syndrome, for finding the specific underlying cause of HF, assessing the severity and prognosis of HF, and identifying patients likely to respond to specific treatments. HF does not occur as a result of a single pathophysiologic disease, but a multiple of pathophysiologic mechanisms resulting in volume and/or pressure overload. This makes the use of these biomarkers complex and difficult. Despite significant overlaps,

Biomarkers	
(1) Myocardial stress/injury	
• Myocardial stress	NT-proBNP, BNP, MR-proBNP
• Myocardial injury	Troponin, heart-type fatty-acid protein
• Oxidative stress	Myeloperoxidase, uric acid
(2) Neurohormonal activation	
• Renin angiotensin system	Renin, Angiotensin II, Aldosterone
• Sympathetic nervous system	Norepinephrine, chromogranin A, adrenomedulin
• Arginine vasopressin system	Arginine vasopressin, copeptin
• Endothelins	ET-1
• Parathyroid	Parathyroid hormone
(3) Remodeling	
• Inflammation	C-reactive protein, osteoprotegerin, TNF-alfa, IL-6, adiponectin
• Hypertrophy/fibrosis	ST-2, galectin-3
• Apoptosis	GDF-15
• Miscallenous	microRNA
(4) Comorbidities	
• Renal biomarkers	Kreatinin, BUN, eGFR, cystatin C, beta-trace protein
• Hematologic biomarkers	Hb, Htc, iron deficiency (ferritin, transferrin saturation), RDW
• Liver function tests	AST, ALT, LDH, Albumin

ALT, Alanine aminotransferase; AST, aspartate aminotransferase; BNP, brain natriuretic peptide; BUN, blood urea nitrogen; ET-1, endothelin 1; Hb, hemoglobin: Htc, hematocrit; IL-6, interleukin-6; LDH, lactate dehydrogenase; MR-proADM, mid-regional proadrenomedullin; MR-proBNP, mid-regional proBNP; NT-proBNP, N-terminal proBNP; RDW, red blood cell distribution width.

Table 1. Biomarkers in heart failure.

biomarkers used in HF can be roughly arranged into four categories: (1) myocardial stress/injury, (2) neurohormonal activation, (3) remodeling, and (4) comorbidities (**Table 1**).

3. Biomarkers for heart failure

3.1. Myocardial stress/injury

3.1.1. Natriuretic peptides (NPs)

In this group, there is robust evidence for both brain natriuretic peptide (BNP) and NT-proBNP regarding HF. The most potent inducer of release of BNP from the left ventricle is left ventricular (LV) wall stretch from increased pressure or volume. A prohormone (proBNP) is degraded to BNP and NT-proBNP, forming three distinct subtypes in the circulation as BNP, NT-proBNP, and proBNP. BNP acts on natriuretic peptide receptor system resulting in natriuresis, diuresis, vasodilation, inhibition of renin and aldosterone, and inhibition of fibrosis [2]. BNP is cleared from circulation by a receptor-mediated mechanism as well as degradation by neutral endopeptidases such as neprilysin. The half-life of BNP is significantly shorter than that of NT-proBNP (approximately 20 vs. 60–120 minutes). Conventional assays for BNP detect proBNP and BNP, as well as various degraded fragments of BNP, while NT-proBNP assays detect NT-proBNP and proBNP [3].

Analytical studies have shown that ratio of BNP to proBNP may have superior prognostic value compared to single BNP assay [4]. In a normal healthy individual, BNP and NT-proBNP serum levels are low, but in a HF patient, serum levels rise proportionately to excess volume overload. The Breathing Not Properly Multinational Study demonstrated that the optimal cutoff value of BNP to diagnose HF was 100 pg/mL, with high accuracy at 85% [5]. Similar findings were seen for NT-proBNP in the ProBNP Investigation of Dyspnea in the Emergency Department (PRIDE) Study in which elevated NT- proBNP concentrations were the strongest predictor of HF compared with traditional assessment [6].

Based on accumulating evidence, BNP and NT-proBNP have been generally used for the differential diagnosis of acute dyspnea [7]. These two peptides have especially high negative predictive value; therefore, they have been generally used for exclusion of HF. The exclusion thresholds of these peptides are different in acute HF in the emergency department than chronic HF in the outpatient setting. For patients presenting with acute onset HF, the optimal exclusion cutoff point is 300 pg/ml for NT-proBNP and 100 pg/ml for BNP, whereas the exclusion cutoff values are 125 and 35 pg/ml, respectively, in the outpatient setting. The sensitivity and specificity of BNP and NT-proBNP for the diagnosis of chronic HF are lower in the outpatient setting [8]. Natriuretic peptide levels increase with age. Therefore, age-stratified cutoff points for NT-proBNP (≥450 for ages <50 years, ≥900 for 50–75 years, and ≥1800 pg/ml for >75 years) performed the best diagnostic accuracy (**Table 2**) [7]. The negative predictive values are high in both acute and non-acute outpatient settings, but the positive predictive values are lower in both situations. Therefore, the use of NPs is recommended more to rule out HF, but not to establish the diagnosis.

Acute HF		Sens.	Spec.	PPV	NPV
BNP	<100 pg/ml	90%	76%	79%	89%
NT-proBNP, overall	<300 pg/ml	99%	68%	62%	99%
NT-proBNP, age-stratified approach		90%	84%	88%	66%
	<450 pg/ml for <50y				
	<900 pg/ml for 50–75y				
	<1800 pg/ml for >85y				
Outpatient screening for symptomatic HF					
BNP	<35 pg/ml	—	—	—	96%
NT-proBNP	<125 pg/ml	—	—	—	98%

BNP, brain natriuretic peptide; HF, heart failure; NPV, negative predictive value; PPV, positive predictive value; Sens., sensitivity; Spec., specificity.

Table 2. Natriuretic peptide exclusion threshold cutoff points (modified from reference 7).

There are some shortcomings of natriuretic peptide biomarkers. HF is not the only disease that increases these peptides. Other diseases that can cause a rise in natriuretic peptides are as follows: acute coronary syndrome, myocarditis, valvular heart disease, hypertrophic cardiomyopathy, cardiotoxic drugs, atrial fibrillation, or flutter and pulmonary embolism. Other conditions that are associated with higher BNP or NT-proBNP levels may be related to comorbidities such as advanced age, renal dysfunction, stroke, and high-output states. HFpEF is associated with lower than expected natriuretic peptide levels compared with HFrEF. The other condition which is associated with lower than the expected NP level is obesity. The explanation for this is suppression of natriuretic peptide synthesis or release in obese people. Therefore, the diagnostic sensitivity of NPs in obese patients is modestly lower. With respect to HFpEF, the same cutoff points for BNP or NT-proBNP can be utilized to diagnose HF with the understanding that the sensitivity is somewhat decreased and HFpEF is associated with lower NP levels compared to HFrEF [9]. Apart from BNP and NT-proBNP, another natriuretic peptide called mid-regional proANP (MR-proANP) has been tested in a large prospective trial [10]. In this large trial, MR-proANP was reported to be a better biomarker in conditions like obesity and chronic renal failure where BNP and NT-proBNP could be less reliable. It has also a diagnostic utility in acute HF same as BNP and NT-proBNP.

Natriuretic peptides are, to date, the best predictors of prognosis in HF. HF therapies, both disease-modifying agents like angiotensin-converting enzyme inhibitors (ACEi), beta-blockers (BB), and mineralocorticoid receptor antagonists (MRA) and diuretics, reduce these NP levels. This observation has led to the concept of biomarker-guided HF management using BNP or NT-proBNP. However, there is inconsistent data regarding the benefit of natriuretic peptide-guided therapy to reduce the mortality and cardiovascular outcomes. Because of this, serial measurement of NPs during treatment of HF did not find a high level of recommendation in the guidelines. Despite this lack of evidence, serial measurement of NPs, at least one at admission and one at predischarge, was used during management of hospitalized patients.

And, the best outcomes for these patients were seen when NP levels decreased by >30% [11]. This predischarge NP level may also be used as a point of reference (i.e., optivolemic NP level) when the patient presents to the emergency department again to aid the clinician for the judgment of hospitalizing the patient later. As a result, in patients admitted with acute decompensated HF, both absolute NT-proBNP discharge levels and a relative reduction of >30% in NT-proBNP levels from admission are significant predictors of readmissions and mortality [12]. However, in the setting of chronic HF patients, the gain that is made by NP-guided treatment has been modest [13].

3.1.2. Myocardial injury

Beyond their ability to diagnose myocardial infarction, troponin T (TnT) and troponin I (TnI) are frequently detectable in HF without obvious cause of ischemia. Elevations in either troponin I or troponin T levels in the setting of acute HF are of prognostic significance and must be interpreted in the clinical context [14]. In the ADHERE registry, 6.2% of patients with acute decompensated HF had an elevated troponin which was associated with worse in-hospital mortality [15]. As ischemia or myocardial infarction may be the precipitating cause of acute decompensation of HF, new HF guidelines recommend troponin measurement in all patients presenting acutely, in order to exclude or diagnose ischemia as a cause and also to assess prognosis as well [16]. In patients with chronic HF, 92% of patients were found to have measurable or elevated hsTnT (detection limit ≤0.001 ng/mL), and hsTnT >0.012 ng/mL was closely linked with poor clinical outcomes [17].

3.2. Neurohormonal activation

Serum aldosterone levels are increased in severe HF patients (New York Heart Association (NYHA) classes III and IV HF). In mild HF (NYHA classes I and II), serum aldosterone levels are not increased unless RAAS is activated by the excessive use of diuretics, leading to renal hypoperfusion [18]. Serum aldosterone measurement identifies not only HF patients likely to respond mineralocorticoid receptor antagonists but also severe HF patients who will benefit from interventions directed for advanced HF.

The second important response to cardiac dysfunction is the activation of the sympathetic nervous system. Chromogranin A (CgA) is a peptide found in adrenal medulla and a multiple number of endocrine cells. It is an important predictor of sympathetic system activation. CgA is a prohormone and needs to be metabolized in order to become biologically active. Its serum level is associated with HF severity, and it predicts mortality in acute HF. The highest mortality occurs when both CgA and NT-proBNP rise together [19].

Adrenomedullin (ADM) is a peptide hormone with strong hypotensive, natriuretic, and positive inotropic effect. It is secreted from the adrenal medulla and kidney upon pressure and volume overload. ADM causes vasodilation via production of nitric oxide (NO), and its level rises in HF as a compensatory mechanism. Due to its short half-life and circulating in the plasma as protein-bound, measurement of ADM is difficult. Alternatively, measurement of mid-regional proadrenomedullin (MR-proADM) is possible. MR-proADM is a precursor

molecule of adrenomedullin; MR-proADM is elevated in patients with acute and chronic HF and is a strong predictor of mortality and HF hospitalization in addition to BNP or NT-proBNP [20]. The data, up to date, are promising, but the implementation of this biomarker into the clinical practice needs more evidence.

Arginine vasopressin (AVP) is an antidiuretic and vasoconstrictor hormone released from posterior hypophysis upon stimulation by change in plasma osmolality and hypovolemia. Production of AVP increases as a compensatory mechanism in HF. AVP is centrally involved in the regulation of free water clearance and plasma osmolality by regulating absorption of water from the collecting tubules of the kidney. AVP plays a role in HF, particularly in the context of hyponatremia which indicates poor prognosis in HF. Due to its short half-life and instability in laboratory circumstances, measurement of AVP is not practical. Copeptin is a stable C-terminal pro-peptide fragment of AVP. In the Biomarkers in Acute Heart Failure (BACH) trial, the elevated copeptin level strongly predicted mortality, and in those with hyponatremia, the elevated copeptin level was more predictive, even after adjusting for NT-proBNP and traditional variables [21]. In the future copeptin values may be used to guide therapy with vasopressin receptor antagonists; however, such data are not available yet.

Endothelin-1(ET-1) is a hormone released from the endothelium via stimulation by angiotensin II, inflammation, and vascular shear stress. It is responsible for profound vasoconstriction, production of reactive oxygen radicals, and ventricular remodeling. Its relation with pulmonary hypertension has been well known, and now its relation to HF has been suggested [22]. Specific treatment of HF patients with ET-1 antagonists yielded nothing. ET-1 may be used to identify HF patients who will benefit from these specific treatments.

Parathyroid hormone (PTH) is a peptide of 84 amino acids (1–84 PTH). PTH is recognized as a key regulator of mineral metabolism and bone health. Together, in association with vitamin D (vit D), PTH regulates homeostasis of calcium, phosphate, and bone turnover. In the parathyroid gland, PTH is secreted by the chief cells in response to decreased ionized calcium concentration in the blood. The increased PTH level is a well-known condition in patients with chronic renal failure. A growing body of evidence indicates that the progression of HF also leads to secondary hyperparathyroidism (SHPT). Secondary hyperaldosteronism and increased amounts of diuretics used for the relief of the patient in advanced stage of HF bring about secondary hyperparathyroidism, assumed to be caused by increased calcium and magnesium excretion in the urine and feces [23]. Measurement of serum PTH could provide complementary information and a simple biomarker strategy to categorize patients with advanced HF based on increased PTH levels, allowing rapid risk stratification in these patients [24].

3.3. Remodeling

Myocardial remodeling is the pivotal process leading to progressive myocardial dysfunction and risk in HF. While BNP, NT-proBNP, and troponin are all also linked to remodeling risk, other biomarkers are worth mention.

3.3.1. Inflammation

Apart from neuroendocrine and sympathetic nervous system, the immune system, via its pro-inflammatory pathways, has been shown to play a role in the development of adverse remodeling and progression of HF [25]. Therefore, inflammatory mediators have been the center of interest for potential biomarkers in HF. Although they have a prognostic importance, they have shortcomings as well. They are not specific to HF.

C-reactive protein (CRP) is the mostly studied inflammatory mediator in HF. It has been shown to be associated with severity of HF [26]. Although recent studies have confirmed the prognostic value of CRP in HF, because of its increased level in a multiple of conditions and not needing specific treatment makes its use in HF impractical. And, it lost its prognostic significance in models where multiple biomarkers were involved [27].

TNF-alfa increases oxidative stress, hence reduces pumping function of the heart, and is associated with the progression of HF [28]. Interleukin-6 (IL-6) affects the intercellular communication between cardiomyocyte and fibroblasts, and change in IL-6 levels causes cardiac dysfunction by changing the cardiac extracellular matrix. IL-6 has been shown to predict adverse events in HF, but due to the lack of diagnostic specificity, it has not been used generally in clinical practice. Pentraxin-3 is a novel promising inflammatory biomarker. It has been shown to predict adverse events in HF better than CRP [29].

Beta-blockers, RAS antagonists, statins, and immunosuppressants have been found to decrease the levels of cytokines in small clinical studies of patients with HF. However, "immunomodulatory" approaches applied in the double-blind, placebo-controlled studies had neutral or negative effects on hard clinical outcomes of patients with HF [30].

3.3.2. Hypertrophy/fibrosis

ST2 is a member of IL-1 receptor family. It could also be classified under inflammation subtitle. Production of ST2 is strongly induced in the setting of cardiomyocyte or cardiac fibroblast stretch. ST2 is closely involved in LV hypertrophy, fibrosis, and remodeling via its interaction with interleukin (IL)-33, a protein with anti-fibrotic and anti-remodeling properties [31]. Soluble form of ST, designated as sST2, neutralizes protective effects of ST2. Increasing ST2 concentrations (e.g., >35 ng/mL) are powerfully associated with adverse clinical outcomes in HF, and compared with BNP or NT-proBNP, ST2 is not as affected by age, renal function, atrial fibrillation, body mass index (BMI), or etiology of cardiomyopathy (ischemic or not) [32]. In a multivariable model that included traditional markers of risk in acute HF patients, ST2 had independent and additive prognostic information beyond NT-proBNP regardless of left ventricular ejection fraction (LVEF) [33]. In addition, serial measurement of ST2 after acute HF therapy provided incremental information beyond a single value and was superior to that provided by NT-proBNP [34]. sST2 levels may change with specific HF therapies. It was shown that beta-blockers reduce ST2 values, giving the promise of the future use of guided HF therapy using serial measurement of ST2 [35].

Galectin-3 (Gal-3) represents the interconnection between inflammation and fibrosis. It is secreted by activated macrophages and located in the vicinity of fibroblasts. Galectin-3 is involved in the inflammatory pathway following injury and ventricular remodeling via tissue repair, myofibroblast proliferation, and fibrogenesis. Its level starts to increase in the very early stages of HF, and this feature of Gal-3 may be used for the early diagnosis of HF before symptoms occur in the future [36]. Galectin-3 is elevated in patients with acute or chronic HF [37]. Gal-3 predicted mortality better than apelin and NT-proBNp in acute HF, especially in patients with HFpEF [38]. Although Gal-3 is frequently associated with HF risk in univariate analyses, it loses its prognostic significance in multivariate analyses after adjustment for renal function or other biomarkers. Serial measurement of galectin-3 in chronic HF patients may add to a single measurement, but to date, there are no known therapies that can alter Gal-3 values [39].

3.4. Comorbidities

Comorbidities often complicate the natural course of HF with deleterious impact on clinical status, symptoms, and HF progression. Therefore, comorbidities including renal dysfunction, hematologic abnormalities, and liver dysfunction are important markers of poor prognosis in HF.

3.4.1. Renal biomarkers

Renal dysfunction (RD) is a common finding in heart failure (HF) and has emerged as one of the most potent prognostic indicators in these patients [40]. Serum creatinine, estimated glomerular filtration rate (eGFR), and blood urea nitrogen (BUN) are important markers of renal function and provide prognostic information about HF [41]. An elevated admission blood urea nitrogen/creatinine (BUN/Cr) identifies acute HF patients likely to experience improvement in renal function with treatment. However, this improvement seems to be largely transient, and RD, in the setting of an elevated BUN/Cr, remains strongly associated with death [42]. In acute HF, prognosis is worse when both NT-proBNP and low eGFR levels rise.

Cystatin-C and β-trace protein (BTP) performed better than traditional renal markers for determining prognosis in HF, presumably due to an enhanced ability to gauge renal function at milder levels of abnormality [43]. Cystatin-C is a cysteine proteinase inhibitor produced by almost every human cell and secreted into circulation. Its removal occurs only by glomerular filtration, and because of this, it is a prototype indicator of renal function. It is not affected by age, gender, and muscle mass. Although cystatin-C was a bit more superior to eGFR for showing renal function, it is far more superior than eGFR for predicting prognosis in HF. Cystatin-C shows not only abnormal renal function but also inflammation and severity of HF as well as predicts mortality and morbidity in acute HF [44].

β-trace protein (BTP) is a novel indicator of renal function. Like cystatin-C, it is also found to be a better predictor of prognosis in HF [43]. It is a low molecular weight protein produced by a wide array of tissue, and it indicates worsening of kidney function. It gives additional prognostic information on top of NT-proBNP in acute HF [45]. Although both cystatin-C and BTP give promise for the guidance of HF management, they have not been used in clinical practice yet.

3.4.2. Hematologic biomarkers

Hematologic abnormalities including anemia, iron deficiency, and increased red blood cell distribution width (RDW) are rather frequent in HF patients and of importance in determining prognosis regardless of LVEF [46].

One of the largest HF registries has clearly demonstrated an independent association between lower hemoglobin values and mortality and morbidity in HF [47]. Although anemia is a common and ominous sign in HF, its treatment did not bring benefit in HF [48].

Iron deficiency (ID) is also a common comorbidity of patients with HF. It is the most frequent cause of anemia in patients with HF, but, most importantly, ID also occurs in non-anemic patients with HFrEF. The presence of ID, regardless of concomitant anemia, has been linked to high mortality and morbidity in HFrEF [49]. Unlike anemia, treatment of ID with intravenous iron therapy in HFrEF patients showed reduced hospitalization rates and improved HF symptoms, exercise capacity, and quality of life [50]. Ferritin and transferrin saturation may be used to identify iron-deficient patients with HFrEF likely to benefit from intravenous iron therapy.

Red blood cell distribution width (RDW) is another important hematologic biomarker in HF, and its prognostic significance is more than hemoglobin in chronic HF [51]. RDW had also been associated with an adverse outcome in acute HF [52]. Higher RDW was associated with HF hospitalizations in the general population as well [53]. RDW is believed to indicate combined inflammation and deranged iron metabolism in HF. Treatment response to high RDW has not been known yet; however, since being cheap and easily applicable, studies searching benefits of treatment targeting RDW should be focused.

3.4.3. Future directions

As discussed above, most of the features described for biomarkers in HF relates to prognostication. We have discussed that prognostic value of a biomarker is only useful if it shows specific change in clinical practice; such change should also translate into improvement in prognosis. This is somewhat accomplished for NT-proBNP and iron deficiency. However, for all other biomarkers, it remains unclear if specific therapy changes should be made in response to an abnormal result. The precision medicine will usher in the future based on the multiple biomarker strategy underpinning the diagnostic and prognostic certainty.

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