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Influence of Serum Biomarkers in the Diagnostic, Prognostic and Therapeutic Management of Patients with Heart Failure

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ABSTRACT

Heart failure (HF) is a clinical syndrome caused by a structural and/or functional cardiac abnormality, resulting in a reduced cardiac output and/or elevated intra-cardiac pressures at rest or during stress. HF continues to be a significant cause of morbidity and mortality worldwide, and over a half of patients with acute HF admitted to the hospital have a history of coronary heart disease. In addition, a substantial proportion of hospitalized patients with coronary heart disease develop acute HF during the hospital stay, and have a worse prognosis in those patients who develop acute HF at the initial presentation. Given the diversity of clinical presentations, several different physio-pathological mechanisms along with triggering factors of circulatory decompensation are involved. The improvement in clinical assessment of HF patients by the utilization of noninvasive and biologically meaningful serum biomarkers has considerably paved the way on HF diagnostic and therapeutic management. Indeed, serum biomarkers allow safe, objective, and biologically relevant insight that complements clinical findings of HF patients. They are useful for determining diagnosis, prognosis, or therapy decision making. There are different biomarkers that can be measured during the evolution of HF, as well as, several pathways involved in HF progression. Therefore, it may be rational to utilize a multi-biomarker measurement approach to individualize the diagnosis, prognosis and therapeutic management in patients with heart failure.

KEYWORDS

Heart failure; Serum biomarkers; Natriuretic peptides; Galectin; MicroRNA.

INTRODUCTION

The number of heart failure (HF) patients is around 23 million people worldwide and it is expected to grow as the population ages due to improved survival and advanced therapies for cardiovascular diseases [1-3]. HF is a clinical syndrome caused by a structural and/or functional cardiac abnormality, resulting in a reduced cardiac output and/or elevated intra-cardiac pressures at rest or during stress [4-7]. HF continues to be a significant cause of morbidity and mortality worldwide, and over a half of patients with acute HF admitted to the hospital have a history of coronary heart disease [8-15]. Acute coronary syndrome complicated by acute HF leads to a several-fold increase in hospital mortality compared to those without acute HF. In addition, a substantial proportion of hospitalized patients with coronary heart disease develop acute HF during the hospital stay, and have a worse prognosis in those patients who develop acute HF at the initial presentation [16-20]. Given the diversity of clinical presentations, several different physio-pathological mechanisms along with triggering factors of circulatory decompensation are involved.

The improvement in clinical assessment of HF patients by the utilization of noninvasive and biologically meaningful serum biomarkers has considerably paved the way on HF diagnostic and therapeutic management. Therefore, we analyzed the role of several serum biomarkers in different ways, namely, to predict the onset of future episodes of HF, to identify the pres-

ence of early or decompensated HF, to risk stratify affected patients, and to guide HF treatment.

THE NATRIURETIC PEPTIDES

The natriuretic peptides represent the gold standard for biomarkers in HF. The understanding about the biology of the natriuretic peptides, and their clinical use has grown exponentially since their introduction. Several structurally similar natriuretic peptides have been identified: atrial natriuretic peptide (ANP), urodilantin (an isoform of ANP), B-type natriuretic peptide (BNP), C-type natriuretic peptide and Dendroaspis natriuretic peptide [21]. ANP and BNP are produced in the myocytes of the atria and ventricles, respectively in response to myocardial stretch due to pressure or volume overload [22, 23]. The biological functions of these natriuretic peptides include natriuresis, diuresis, and vasodilation [24-26].

During HF because of myocardial stretch, the induction of the BNP gene results in the production and secretion of prohormone proBNP1–108. This is cleaved into the biologically active BNP, as well as, NT-proBNP which is biologically inert, but biochemically more stable. Both fragments are detected in plasma [27]. The Breathing Not Properly Study measured BNP levels in 1586 patients with acute dyspnea [28]. Those patients with clinically diagnosed HF had higher BNP levels compared with those without HF (mean 675±450 vs 110±225 pg/mL, p<0.001). BNP was the best single predictor of a final diagnosis of HF compared to other clinical findings [28]. NT-proBNP is cleared via different mechanisms and has a longer half-life than BNP (70 min vs. 20 min). The use of NT-proBNP in the diagnosis of acutely decompensated HF was first demonstrated in the ProBNP Investigation of Dyspnea in the PRIDE Study [29]. Later on, the International collaborative of NT-proBNP (ICON) study investigated 1256 acutely dyspneic patients [30]. They found that decompensated HF patients had higher NT-proBNP concentrations, compared to those patients without HF (4639 vs. 108 pg/mL, p<0.001) [30]. The use of BNP and NT-proBNP for the diagnosis of HF has dramatically impacted the standard of care in HF and the therapeutic management. All major societies worldwide recommend the use of BNP or NT-proBNP for the diagnosis of HF in their clinical practice guidelines [31, 32].

OTHER SERUM BIOMARKERS IN HEART FAILURE

Several different serum biomarkers have been studied, such as mid-regional pro atrial natriuretic peptide (MR-proANP), mid-regional pro adrenomedullin (MR-proADM), highly sensitive troponins, soluble ST2 (sST2), growth differentiation factor (GDF)-15, Galectin-3, and microRNA, show potential in evaluate HF diagnosis, prognosis and treatment [21-38].

Adrenomedullin (ADM) is another serum biomarker that can be very useful in HF [33-36]. Circulating levels of ADM are elevated in HF and correlate with decreasing left ventricular ejection fraction, increasing pulmonary artery pressures and the presence of diastolic dysfunction and restrictive filling patterns [35, 36]. ADM was initially found in pheochromocytoma cells in the adrenal medulla and has potent vasodilatory effects. ADM has been also found in other organs including the heart increasing myocardial contractility through a cyclic AMP-independent mechanism [33, 34]. A commercial assay measuring the mid-regional portion of the stable prohormone of ADM, MR-proADM, has been developed and used to explore its role in HF. In the BACH study, MR-proADM was found to have strong prognostic value for death at 90 days [37]. This prognostic value was further corroborated in the PRIDE study [38].

Although cardiac troponins have been used for the diagnostic evaluation for acute coronary syndromes, they are also elevated in HF [39]. Xue et al. demonstrated that concentrations of highly sensitive troponin I (hsTnI) were frequently elevated in patients with acutely decompensated HF [40]. hsTnI typically rose or remained elevated in subjects with impending complications. On the other hand, ST2, another serum biomarker was found to have prognostic value in patients with acutely decompensated HF [41, 42]. ST2 was found to have immunomodulatory function as a cell-surface marker of T helper type 2 lymphocytes. ST2 was found in the context of cell proliferation, inflammatory states and autoimmune diseases [43]. However, the ST2 system is also induced in mechanical strain of cardiac fibroblasts or cardiomyocytes, and it may be involved in cardiac remodeling and fibrosis in HF [44]. A soluble "decoy receptor" version (sST2) was studied in 593 patients presenting with acute dyspnea [41, 42]. It was demonstrated a concentration-dependent relationship between sST2 and many clinical markers of HF severity including left ventricular ejection fraction and NYHA functional classification. An elevated sST2 was prognostic in acutely decompensated HF patients (HR=9.3, p=0.003), and in all dyspnea patients (HR=5.6, p<0.001) in multivariable analyses.

Another interesting serum biomarker that has a role in HF is GDF-15 which is a member of the transforming growth factor-β cytokine superfamily. GDF-15 is induced in cardiomyocytes in response to metabolic stress such as in pressure overload states, hence, it is elevated in HF [45-53]. The Val-HeFT study which included 1734 patients demonstrated the utility of GDF-15 [50]. This serum biomarker was measured at baseline and after 12 months of treatment with the angiotensin receptor blocker valsartan or placebo. In 85% of the patients there were abnormal concentrations greater than 1200 ng/L associated with features of advanced HF. Moreover, GDF-15 was an independent predictor of death (HR 1.007, 95% CI

1.001–1.014) in a multiple-variable Cox regression model that included clinical risk factors, BNP, high-sensitivity C-reactive protein and hsTnT [50].

Galectin-3 is a macrophage product member of the lectin family which is related to the inflammatory cascade following cardiac injury [51]. Galectin-3 was first measured in patients from the PRIDE study [52]. Patients with HF had higher levels of galectin-3 compared with those without HF (median 9.2 ng/mL vs. 6.9 ng/mL, p<0.001). Galectin-3's ability to predict 60-day mortality was superior to NT-proBNP even after adjusting for traditional risk factors. However, similar to other serum biomarkers of prognosis mentioned above, adding galectin-3 to NT-proBNP and other risk factors provided the best strategy for predicting prognosis in HF [52].

In addition, there is also interesting data on functional microRNA (miRNA) from clinical studies which reported that a variety of miRNA play a role in pathogenic mechanisms leading to heart failure, such as remodeling, hypertrophy, apoptosis, and hypoxia [54, 55]. There is strong evidence that miRNAs play a role in the onset and progression of heart failure, and because of their stability in plasma, miRNAs are interesting potential novel biomarkers in heart failure [56-58].

CONCLUSION

In conclusion, serum biomarkers allow safe, objective, and biologically relevant insight that complements clinical findings of HF patients. They are useful for determining diagnosis, prognosis, or therapy decision making. There are different biomarkers that can be measured during the evolution of HF, as well as, several pathways involved in HF progression. Therefore, it may be rational to utilize a multi-biomarker measurement approach to individualize the diagnosis, prognosis and therapeutic management in patients with heart failure.

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