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Biomarkers and heart disease

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Abstract. – Heart failure (HF) results from the impaired ability of heart to fill or pump out blood. HF is a common health problem with a multitude of causes and affects ~30 million people worldwide. Since ageing is a major risk factor for HF and as several treatment options are currently available to prolong the patients' survival, the number of affected patients is expected to grow. Even though traditional methods of assessment have been in use for managing HF, these are limited by time consuming and costly subjective interpretation and also by their invasive nature. Comparatively, biomarkers offer an objective and biologically relevant information that in conjunction with the patients' clinical findings provides optimal picture regarding the status of the HF patient and thus helps in diagnosis and prognosis. The current gold standard biomarkers for the diagnosis and prognosis of HF are B-type natriuretic peptide (BNP) and N-terminal proBNP (NT-proBNP). Additional novel biomarkers (e.g., mid-regional pro atrial natriuretic peptide (MR-proANP), mid-regional pro adrenomedullin (MR-proADM), troponins, soluble ST2 (sST2), growth differentiation factor (GDF)-15 and galectin-3) can potentially identify different pathophysiological processes such as myocardial insult, inflammation and remodeling as the causes for the development and progression of HF.

Different biomarkers of HF not only reflect the underlying mechanisms/pathways of HF and also its progression and also point specific therapy options. A multi-biomarker approach for personalized medical care is not too far fetched and such approach can greatly enhance diagnosis, prognostication, and therapy guidance for HF. In this review we describe the current status of HF biomarkers in clinical use and in laboratory research and the efforts aimed at the identification of novel biomarkers for HF.

Key Words:
Heart failure, Biomarkers, B-type natriuretic peptide (BNP), N-terminal proBNP (NT-proBNP), Troponins, Mid-regional pro adrenomedullin (MR-proADM).

Introduction

Heart failure (HF) results from the inability of heart to function properly, which is commonly seen in a number of cardiovascular disorders. It is estimated that more than 23 million people will die due to cardiovascular disorders annually by the year 2030[1]. As the treatment choices are improving to control mortality due to HF, the ageing population that suffers from HF is constantly on the rise and thus adding a substantial burden on health costs. The symptoms for HF are often nonspecific, for example, dyspnea, orthopnea, paroxysmal nocturnal dyspnea, fatigue, weakness and exercise intolerance can be due to either congestion or because of inadequate cardiac output, thus, making diagnosis difficult by clinical presentation alone and also delayed definitive diagnosis and poor prognosis[2]. Normally, a patient with suspected HF is evaluated on the basis of clinical assessment, history, physical examination and chest x-ray, despite the fact that isolated symptoms and signs often do not correlate with these objective methods. Many of the clinical criteria suffer from limited sensitivity and/or specificity. Noninvasive imaging approaches, e.g., echocardiography and radionuclide angiography, can be helpful to identify or exclude HF as these techniques can determine ventricular ejection fraction and diastolic dysfunction, and also estimate the chamber pressures. However, false positives can be an issue as many patients with abnormal ventricular systolic function on imaging studies are asymptomatic and do not necessarily have the clinical syndrome of HF[3].

While a number of disease management approaches ranging from nursing-based interventions to technological interventions using implantable hemodynamic monitors and telemedi-

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cine, have been evaluated to improve the health status of chronic heart failure patients, the success of these approaches is limited because these approaches are involved, complex, or expensive to implement[4]. Biomarkers can reflect a patient's biology and they can provide objective and accurate information, their use has emerged as a promising and cost-effective diagnostic method to facilitate therapeutic decision-making[5].

Methods

This Review was compiled from a literature search using the PubMed database, Google Scholar as well as other publicly available databases. Full-text articles and reviews published in English within the past 20 years were searched using terms, "heart failure and biomarkers", "renal dysfunction and heart failure and biomarkers", and "therapeutic implications of biomarkers in heart failure".

Biology of Biomarkers and Heart Failure

Biomarkers of heart failure typically refer to proteins and/ or other substances – measured in patients' blood and these are different than the commonly used laboratory tests like sodium, red blood cell distribution width and albumin and imaging tests such as transthoracic echocardiograms. Components of several pathways related to regulation of neurohormonal system, ventricular dysfunction, cardiac remodeling and myocardial injury are likely to appear in circulation and their levels may alter with the progression of heart failure. Thus the changes in the concentration of some of these components can be used as potential biomarkers for diagnosing the progression of disease. Depending on the type of molecules that are changing, the pathways that are most responsible for the disease progression can be deciphered (Figure 1). HF is a complex syndrome where a number of pathways are disturbed, and is a mixture of several distinct disease sub-types. An ideal prognostic biomarker in HF not only should make it possible for early identification of individuals at risk for adverse clinical outcomes but also should be relatively easy to measure accurately[6].

Among the biomarkers that are considered for clinical use only the natriuretic peptides meet the proposed standards at present. Most of the remaining biomarkers are not yet considered established as to whether they provide any reliable clinical measurements towards the diagnosis/ prognosis of HF[7]. Among the more validated and currently in use biomarkers, B-type natriuretic peptide (BNP) and N-terminal proBNP (NT-proBNP), are prominent, while other markers are still being assessed for potential clinical use[8]. The 2013 ACC/AHA Guidelines for the management of HF, recommended natriuretic peptides as Class I for diagnosing and establishing prognosis in chronic heart failure, and a Class IIa recommendation for guidance of evidence based treatments[4]. Furthermore, studies such as PRIDE (ProBNP Investigation of Dyspnea in the Emergency Department), also recommended natriuretic peptide assessment for diagnosis of heart failure in the setting of clinical uncertainty at the highest level[4]. Recently FDA cleared two novel biomarkers galectin-3, and ST2 for use in chronic heart failure (Table I). Plasma norepinephrine levels have been useful as independent predictors of mortality and it has been noted that angiotensin II, aldosterone, and norepinephrine levels not only increase in heart failure patients, but they decrease with enalapril therapy[9]. The Valsartan Heart Failure Trial (Val-HeFT) also found BNP, norepinephrine, renin, and aldosterone levels to be elevated and to have important prognostic value in 4300 chronic heart failure patients[10]. Other promising neurohormone biomarkers of HF that have potential prognostic value, include endothelin-1 (ET-1) and peptide arginine vasopressin (AVP), which also play a role in HF[11]. However, because of plasma instability, the clinical use of these neurohormones is limited and more stable forms of ET-1 and AVP, have been described recently and these are C-terminal pro-endothelin-1 (CT-proET-1) and copeptin, respectively, that are synthesized and secreted in equimolar amounts as the biologically active proteins[12]. Recent studies on the importance of biomarkers in predicting cardiac hospitalizations showed that the strongest associations with hospitalization were seen with BNP and troponin I (TnI), whereas etiology dependent associations for the remaining biomarkers suggest etiology-specific mechanisms for HF exacerbation. Soluble fms-like tyrosine kinase receptor-1 (sFlt-1) appeared to be a potential role as a biomarker of HF morbidity as this biomarker showed strong association with cardiac hospitalization[13].

Inflammation Related Markers

Inflammation has been known to play a role in chronic HF since 1954 when it was discovered

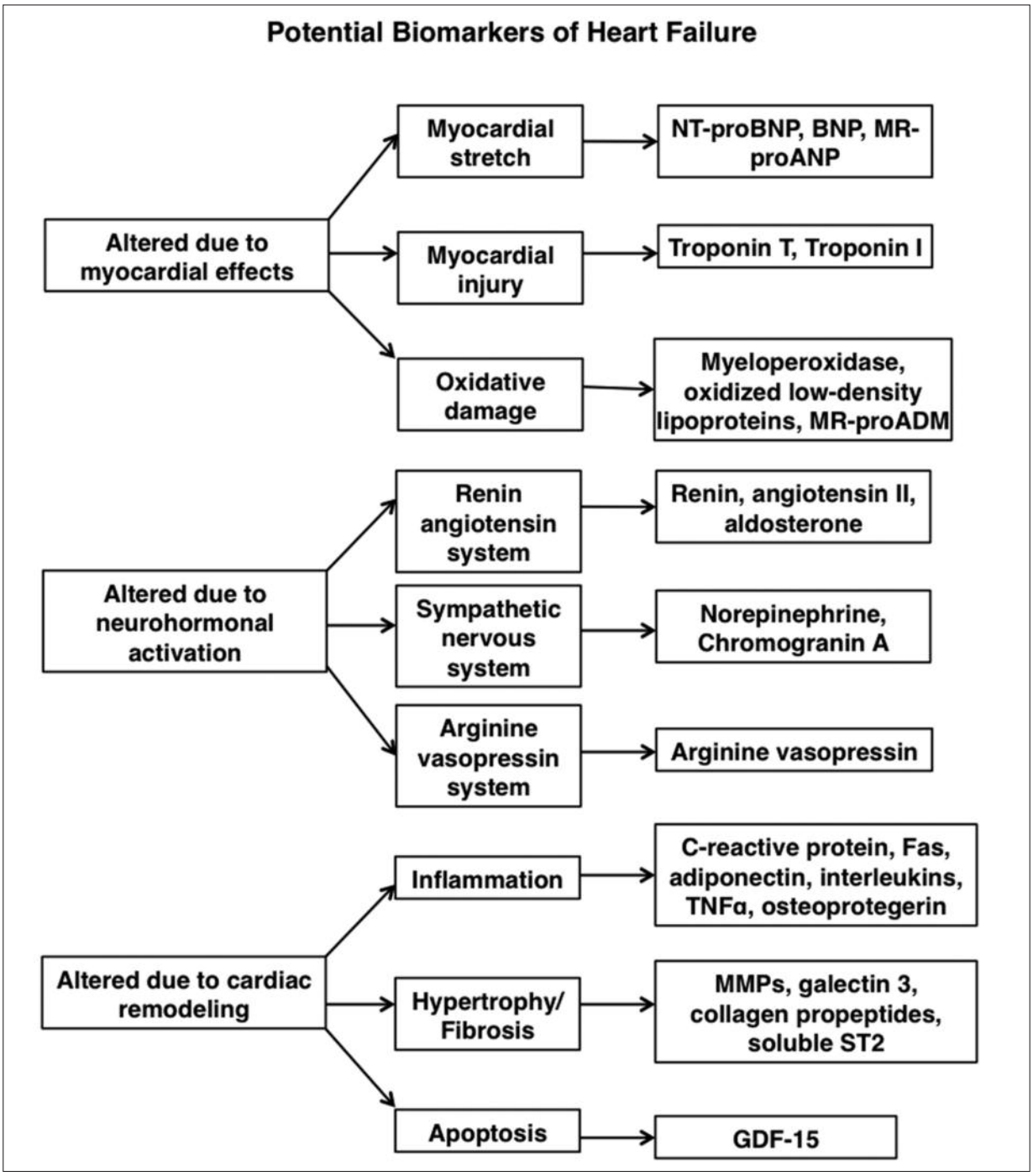

Figure 1. Potential Biomakers of heart failure.

that plasma levels of C-reactive protein are elevated in HF patients[14]. Further work revealed increases in the plasma levels of other important inflammation markers including tumor necrosis factor (TNF-a) and other members of the TNF superfamily (e.g. osteoprotegerin), interleukins, pentraxin-3, and procalcitonin[15]. Recently, certain markers of inflammation, which are elevated in plasma, have been shown to have significant prognostic and therapeutic implications in HF. It is hypothesized that HF precipitating events such as acute coronary syndromes likely trigger an innate stress response, which leads to elevated plasma levels of proinflammatory cytokines that

further aggravate cardiac dysfunction[16]. In the future, Plasma levels of these inflammation-related markers will likely prove useful in future towards the development of novel anti-inflammatory therapies for HF patients. These markers include growth differentiation factor (GDF)-15, a member of the transforming growth factor family, which is induced by myocardial stress[17,18]. GDF-15 participates in mitigation of myocardial stress and remodeling and its expression in cardiomyocytes is induced in response to cardiac ischemia (nitric oxide-dependent) or pressure overload state (angiotensin 2-dependent)[19]. It has been observed that GDF-15 levels are elevated in acute myocardial infarction and HF[18] (Table I).

Galectin-3, a member of the lectin family, is found on a wide variety of cells and tissues surfaces. It may have functions related to the inflammatory cascade following cardiac injury, and also pathways regulating cardiac contractility[20].

Table I. Selected heart failure biomarkers: their implication in therapeutic application.

Biomarker	Proposed Pathophysiology	Potential Therapeutic Role
CT-proET-1	Stable surrogate for endothelin-1. Promotes vasoconstriction and adverse vascular remodeling via renin–angiotensin system and stimulation of sympathetic nervous system.	Prognostic marker; use in therapeutic guidance.
BNP/ NTproBNP	Released from ventricles in response to mechanical stretch. Leads to arterial vasodilation.	Diagnostic and prognostic marker; used as therapeutic guide.
sST2	Cardioprotective paracrine signaling system, activated mechanically; shields the myocardium against the effects of overload.	Prognostic marker; use in therapeutic guidance and also a potential therapeutic target.
MR-proADM	Made within the cardiovascular system in response to hemodynamic stress and exerts favorable effects on the vasculature.	Prognostic marker; use in therapeutic guidance.
Galectin-3	β-galactoside-binding lectin and promotes maladaptive cardiac remodeling.	Prognostic marker; use in therapeutic guidance. Potential role in anti-fibrotic therapies.
GDF-15	A TGF-β cytokine family member and its myocyte expression is triggered by inflammation, ischemia, stretch, and neurohormonal activation.	Prognostic marker; use in therapeutic guidance. Role in anti-inflammatory therapies.
hs-Troponin	Involved in cardiac and skeletal muscle contraction. Released into plasma due to myocardial injury, necrosis and apoptosis.	Prognostic marker; use in therapeutic guidance.
KIM-1	Expressed in proximal renal tubules as transmembrane glycoprotein and released in response to kidney injury.	Prognostic marker; Role in therapeutic guidance via early detection of cardio-renal syndrome.
Cystatin-C	Produced by most cells; a cysteine protease inhibitor that is more sensitive and specific to changes in glomerular filtration rate than creatinine.	Prognostic marker; Role in therapeutic guidance via early detection of cardio-renal syndrome.

Even though patients with HF show higher levels of galectin-3 in comparison to those without HF, NT-proBNP outperformed galectin-3 for the diagnosis of HF[21]. However, galectin-3 was far better than NT-proBNP in predicting 60-day mortality in HF patients, even after adjusting for traditional risk factors. Plasma concentrations of galectin-3 were found to be prognostic in patients with chronic, ambulatory HF[21].

Biomarkers of Myocardial Stretch

The idea of myocardial stretch biomarkers was first suggested by the observation that rat atrial extract had a potent diuretic effect[22]. Subsequent work identified that pre-prohormone BNP, synthesized in the cardiomyocytes when the ventricles are stressed and cleaved to two polypeptides: NT-pro-BNP and BNP, both of which are clinically useful biomarkers. In fact, elevated levels of these two peptides have been found to be powerful predictors of adverse outcomes of HF[23]. ST2, another marker, was first discovered in cultured myoctyes as a mechanically induced gene product[24] and clinical studies indicated ST2 to be a strong predictor of adverse outcomes in chronic heart failure, independent of natriuretic peptide levels[25]. ST2, is a member of the IL-1 receptor family and exists as soluble as well as membrane bound form in cardiomyocytes and endothelial cells together with its ligand IL-33, and these two form a mechanically activated cardioprotective paracrine signaling system, which protects the myocardium against adverse effects of overload[25]. In a recent study with 813 ambulatory systolic HF patients, it was observed that biomarkers of myocardial stress and fibrosis were strong independent predictors of death from pump failure and sudden cardiac death and that when considering individual patient risk, models comprising of clinical factors and NT-proBNP levels were stronger predictors of pump failure than sudden cardiac death[26].

Plasma levels of BNP and NT-proBNP typically fall with therapies that are effective to improve mortality in HF patients, such as therapy with beta blockers[27], angiotensin converting enzyme inhibitors[28], angiotensin II receptor blockers[29] and aldosterone antagonists[30]. A decreasing trend in natriuretic peptide levels predicts a favorable prognosis and the effectiveness of the therapy in place.

Adrenomedullin (ADM)

ADM, originally discovered in pheochromocytoma cells of adrenal medulla shows potent vasodilatory effects and this peptide has been found in different organs including the heart, where it elevates nitric oxide synthesis under conditions where cytokine production is increased and also myocardial contractility in a cyclic AMP-independent manner[8]. In patients with HF circulating levels of ADM are elevated and correlate with decreased left ventricular ejection fraction, increased pulmonary artery pressures and diastolic dysfunction and restrictive filling patterns[31]. Besides, infusion of ADM in patients with HF causes vasodilation, increases cardiac index and reduces of pulmonary capillary wedge pressure[32]. Overall, ADM release into circulation probably reflects a compensatory mechanism in HF. While ADM per se is difficult to measure, methods have been developed for assaying the mid-regional portion of the prohormone of ADM, MR-proADM, which is relatively more stable, and used to explore its role in HF. Several studies have authenticated the prognostic power of MR-proADM biomarker, for HF related deaths and this proved to have better predictability than the natriuretic peptides[33,34].

Cardiac Troponins as Markers of Myocardial Injury

Cardiac troponins have been biomarkers of choice for the diagnosis acute myocardial infarction (MI). However, cardiac troponins are elevated in other heart related disorders including HF[35]. Troponin release in HF can be due to MI types 1 and 2, in the presence or absence of coronary artery disease respectively, cytotoxicity, apoptosis, and also inflammation. Elevated troponin levels in patients with HF are strongly prognostic. As more sensitive troponin (hsTn) assays became available, myocardial necrosis is now readily detected in most patients with HF syndromes, adding much prognostic value for this biomarker.

Renal Dysfunction

Hemodynamics management and maintenance of fluid status in health and disease is achieved by a cross talk between heart and kidneys. Renal sodium and water retention leads to fluid retention and is central to the clinical symptoms of chronic HF. It is well known that many medications cause kidney injury, leading to more dysfunctional cardio-renal axis, and higher rates of mortality and morbidity[5]. Thus biomarkers that can accurately predict and provide information about renal dysfunction can be useful in the diagnosis/ prognosis of HF. Bio-

markers of renal injury that are not only more sensitive but also specific to changes in glomerular filtration rate may lead to early stage therapeutic intervention thus preventing further damage to the kidneys[36]. Among these, four renal biomarkers were found to provide unique information about kidney injury and also they have been shown to provide significant prognostic information about patients with chronic HF[37,38]. These biomarkers are Cystatin C (CysC), Neutral gelatinase-associated lipocalin (NGAL), N-acetyl-beta-D-glucosaminidase (NAG), and Kidney injury molecule-1 (KIM-1). CysC, a cysteine protease inhibitor is a product of a 'housekeeping' gene and is produced by all nucleated cells of the body. NGAL is a small glycoprotein released by epithelial cells, renal tubular cells, and also hepatocytes, during inflammation or following injury[39]. NAG, a lysosomal enzyme, is formed in the proximal tubule of kidneys and is elevated in the urine after injury[40]. KIM-1, a transmembrane glycoprotein, is also expressed in the proximal renal tubules, and is released in the urine, after injury[41]. The prognostic value of NAG and KIM-1 depends on measurement in urine rather than plasma samples, as their levels change more dramatically in the urine following renal injury. Further studies directed to understand the role of these biomarkers in monitoring renal response to heart failure therapy, are needed and also to ascertain their additional predictive value when used alongside other biomarkers.

Type 1 Collagen and Myocardial Fibrosis

It is known that increased deposition of collagen in the extracellular matrix of the heart causes fibrosis and structural remodeling[42] and myocardial fibrosis in turn results in impaired cardiac function and increases the risk of developing myocardial infarction and heart failure[43]. Myocardial fibrosis is due to disturbed balance between synthesis and degradation of collagen types I and III fibers, with the resultant increase in collagen levels. The C-terminal propeptide of procollagen type I (PICP) is a biomarker of myocardial collagen type I synthesis, whereas the C-terminal telopeptide of collagen type I (CITP) is a marker of type 1 collagen degradation and these markers reflect the extent and severity of interstitial and perivascular fibrosis in the heart[44]. Biomarkers of type I collagen synthesis (PICP) and degradation (CITP) are independently related to indices of left ventricular size and diastolic function in systolic heart failure[42].

MicroRNAs and Their Potential as Biomarkers for HF

Recent studies have shown that microRNAs (miRNAs), which are short, single-stranded and non-coding RNAs, present in human plasma and correlate with various pathologies, as potential disease markers and targets for diagnostic and therapeutic applications, respectively. Heart- and muscle-specific circulating miRNAs (myomirs) were found to be elevated by 140-fold in advanced HF, similar to the increase seen in cardiac troponin I (cTnI) protein levels, the established marker for heart injury[45]. These circulating miRNA changes were almost completely reversed 3 months after initiation of left ventricular assist device support. Besides this, in stable HF, there were < 5 fold differences in circulating miRNAs, whereas myomir and cTnI levels were at the detection limit, as compared with HF free subjects[45]. It has been shown that the dynamic changes in circulating muscle-specific miRNA, miR-133b, reflect early myocardial injury following heart transplantation. It is suggested that miR-133b is a better marker than cTnI in predicting transplanted heart dysfunction and recovery of patients[46].

Multi-Biomarker Approach for Treatment Guidance

Inasmuch as the pathogenesis of HF is most likely due to the collective effect of multiple factors such as myocardial strain, remodeling, inflammation, neurohormonal activation, cardiomyocyte injury, and renal dysfunction and their interactions, an assemblage of biomarkers, i.e., a multimarker approach, can potentially provide a molecular 'fingerprint' of the disease that is complementary to clinical data. Considering the large number of potential biomarkers that could potentially play a role in chronic heart failure therapeutics, more innovative approaches are needed for evaluating the clinical use of these biomarkers. Biomarkers with limited prognostic value in their own right, may still prove worthy of consideration as they may be able to provide valuable information about heart failure pathophysiology, when used as part of an assemblage of multiple markers. Multi-marker approach for the diagnosis and prognosis of heart failure can allow for the integration of various associated aspects of the disease process such as renal disease, inflammation, and myocardial fibrosis, and also provide clinically relevant and therapeutically useful information. Recent studies showed that a

combination of 7 biomarkers with the resultant multimarker score led to much better reclassification of HF patients[47]. Similarly, it has been shown that in older HF patients, addition of CT-proET-1 or MR-proADM to NT-proBNP significantly improved the diagnostic accuracy of acute HF. Either of these dual biomarker approaches could significantly improve risk reclassification as compared to NT-proBNP alone[48]. Another study indicated that in older HF patients who required significantly higher levels of NTproBNP than younger patients for proper risk assessment, inclusion of TnT and CysC and age was found to greatly improve risk stratification for mortality, in particular when NTproBNP was moderately elevated[49].

Conflict of Interest

The Authors declare that there are no conflicts of interest.

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