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An update of biomarkers in heart failure

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Abstract
Cardiac biomarkers are substances that are liberated into the blood as a result of injury or stress to the heart. Biomarkers have 2 vital functions: Firstly, they aid in understanding the pathophysiology of disease, and secondly assist in making diagnosis, prognosis, or treatment feedback. In recent past, biomarker tests have been considered as an elective supplement in diagnosing patients suspicious of heart failure (HF). There is an increasing enthusiasm in the advancement of novel biomarkers, and a large variety of tests have been lately suggested. In this review, we have described a short introduction to these biomarkers along with their recent advances.
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Introduction

There are a number of biomarkers which are used to assess and guide treatment in patients with heart failure (HF). We have described recent breakthrough in the understanding of established biomarkers in HF such as the natriuretic peptides. HF biomarkers have been classified by Braunwald [1] in 2008 into 7 categories according to their pathophysiological effects in HF: inflammation, oxidative stress, extracellular-matrix remodelling, neurohormones, myocyte injury, myocyte stress and new biomarkers. Each of the mentioned biomarkers will be discussed below.

Inflammatory markers

C-reactive protein (CRP)

Among outpatients with stable coronary heart disease, elevated C-reactive protein (CRP) levels predict hospitalization for HF, independent of baseline HF, medication use, disease severity, and ensuing myocardial infarction (MI) events [2]. It can be partly explained by an abnormal diastolic function in patients with high CRP levels. CRP had no prognostic purpose in acute HF patients with an infectious disease [3]. Non infected patients with higher CRP at discharge had worse outcome. High sensitivity CRP (hsCRP) correlates with incident HF in general and in high-risk populations and procures prognostic data in HF patients [4].

Tumor necrosis factor α (TNF-α)

Increased Tumor necrosis factor α (TNF-α) level in patients with recent onset HF are linked to derangement of left atrial function and severe left ventricular dysfunction [5] . TNF α was raised in most of HF patients. It was associated with a large decrease in survival, and provided meaningful information in risk assessment above established indicators. TNF α is important for prognosis in HF patients with preserved and reduced ejection fractions [6].

Pro-apoptotic molecules apoptosis-stimulating fragment (FAS, CD95/APO-1) and tumour necrosis factor-related apoptosis-inducing ligand (TRAIL)

Pro-apoptotic molecules apoptosis-stimulating fragments (Fas) are expressed on a variety of cells, including myocytes. Soluble FAS (sFAS) is a promising biomarker with pathophysiological importance and prognostic competence in HF management [7]. The latter may help to identify patients with elevated risk despite minor level of BNP. In contrast to sFAS, high level of soluble TRAIL (sTRAIL) showed a protective response with a markedly reduced mortality in HF patients. Further studies are required to confirm the actual results and to define cut-off values before its employment in clinical practice.

Interleukins (IL) 1, 6, and 18

High serum level of Interleukin-1 receptor-like 1 (ILRL1) isoform B is firmly connected to poor outcome in HF patients. This link has been proved in various HF cohorts and is independent of etiology, age, and left ventricular function[8]. Eventually IL1RL1 may become a therapeutic target in HF.
IL-1β activity contributes to poor exercise endurance in patients with systolic HF and recognize IL-1β blockade as a new technique in pharmacology [9]. In HF patients, a reverse correlation was observed

between IL-18 values and ejection fraction, mean arterial pressure and body mass index. Raised IL-18 concentrations were related with higher mortality[10].

Oxidative stress

Oxidized low-density lipoproteins (oxLDL) and arylesterase

Oxidized low-density lipoproteins (oxLDL) are an arising prognostic marker in congestive HF [11]. OxLDL antibody titer is valuable in prognosis of HF [12]. In patients with systolic HF, low serum arylesterase level indicates considerable risk of lifelong detrimental cardiac effect autonomous of other traditional risk factors[13].

Myeloperoxidase (MPO)

Myeloperoxidase (MPO) is produced by neutrophils, monocytes, and endothelial cells. Large amount of MPO predict mortality in patients with chronic HF. MPO is an independent predictor of 1-year mortality in acute HF and also additive to BNP [14]. It can be beneficial in pinpointing patients with a favorable prognosis despite raised BNP concentrations.

Extracellular-matrix remodeling

Tissue inhibitors of metalloproteinases (TIMP)

TIMP-1 alone can be used to predict death in patient with stable congestive HF [15].

Collagen propeptides and Plasma procollagen type III (PIIINP)

In HF patients, Collagen propeptides and Plasma procollagen type III (PIIINP) was incomparably linked with heart rate changes. PIIINP is a promising biomarker for evaluation of cardiac autonomic control and the risk of sudden cardiac death in HF patients [16].

Neurohormones

Pro renin receptor (P) RR

Pro renin receptor (P) RR is involved in blood pressure balancing and pathophysiology of HF [17]. In HF patient, blocking of (P) RR resulted in cardiovascular and renal advantages by inhibiting renin-angiotensin-aldosterone pathway. These findings label the receptor as a potential therapeutic target. A significant increase in (P) RR was observed in patients with dilated cardiomyopathy. (P) RR expression is strongly up-regulated failing human heart, hinting to a probable role of (P) RR in cardiac pathophysiology[18].

Arginine vasopressin

Clinical trials with several arginine vasopressin receptor antagonists (termed vaptans) have promising early results in improving dyspnea, increasing urine output, and improving hyponatremia[19]. Raised Copeptin, the C-terminal part of vasopressin, is seen following MI and indicates poor prognosis. Combined use of high sensitivity cardiac troponin and copeptin might predict clinical outcome of patients with chronic stable HF [20].

Endothelin (ET) AND Adrenomedullin

Among different ET-1 receptor antagonists, bosentan and ET-A receptor antagonist, BQ-123; appears to be helpful for management of congestive HF [21]. Adrenomedullin and endothelin-1 are promising biomarkers in chronic HF. According to recent studies ET play important roles in controlling inflammation. Vasoregulation and inflammation may be connected to HF patients independently of the disease severity[22].

Myocyte injury

Cardiac troponins

Cardiac troponins represent markers of myocardial injury that are also detected in a large amount of HF patients[23]. Their levels are associated with an increased risk of morbidity and mortality in HF, thus contributing to additional prognostic information. Cardiac troponins may help assess response to HF treatment and pick out patients requiring minute monitoring and management.

Myosin light-chain kinase (MYL)

Li et al[24]reported down-expression of the Myosin light-chain kinase (MYL2) gene in chronic HF patients. There was down-regulation of MYL2 in patients with moderate HF which was worse in patients with severe HF. These suggest a connection between down-regulation of MYL2 and degree of clinical HF.

Myocyte stress

Brain natriuretic peptide (BNP) and N-terminal pro–brain natriuretic peptide (NT-proBNP)

Among elderly patients with HF, high concentrations of copeptin alone or combined with elevated N-terminal pro–brain natriuretic peptide (NT-proBNP) level were related to greater risk of all-cause mortality [25]. Regulation of therapy using serial Brain natriuretic peptide (BNP) or NT-pro-BNP levels correlated with marked decrease in all-cause mortality in contrast to standard care in patients having chronic HF [26]. In patients with left ventricular systolic dysfunction, NT-proBNP level can indicate the condition of the heart [27]. The use of two biomarkers combination (CRP and BNP) was better than using only one biomarker in estimating risk , but inclusion of a third biomarker (troponin T) did not prove beneficial [6].

Midregional fragment of proadrenomedullin (MR-proADM)

Midregional fragment of proadrenomedullin **(**MR-proADM) is a promising biomarker and has valuable prognosis for mortality and morbidity in patients having HF as a complication of acute MI. MR-proADM had better predictive value than BNP and NT-proBNP[28]. MR-proADM alone or together with NT-proBNP has a potential to benefit physicians in risk stratifying patients suffering from acute dyspnea indifferent of the cause. MR-proADM on admission foresees 30-day and one-year mortality and appears to surpass natriuretic peptides concerning short-period mortality [29].

ST2

Soluble ST2 is a diagnostic and prognostic marker in acute HF. It is a potent marker for risk in chronic HF and when used along with NT-proBNP, prognosis assessment is enhanced [30]. ST2 was considerably associated with outcomes among ambulatory HF patients, but it did not markedly influence risk reclassification [31].

Fresh biomarkers

Chromogranin

High plasma Chromogranin A levels were found in chronic and acute HF and correspond with those of established biomarkers, such as natriuretic peptides and ET-1, and have prognostic significance in indicating degree of the disease as well as mortality[32]. Chromogranin B production is increased in relation to the stage of HF [33].

Galectin-3

Galectin-3 is produced by activated cardiac macrophages. It is elevated in ambulatory HF patients and is linked with deficient functional ability [34]. Galectin-3 was markedly prognosticative of long-standing outcomes, but this correlation was not constant after titration of other biomarkers, particularly NTproBNP.

Osteoprotegerin (OPG)

Osteoprotegerin (OPG) is predictive of death and hospitalization for HF after acute coronary syndrome [35]. In patients with congestive HF, OPG was independently associated with mortality. OPG alone predicted worsening HF hospitalization in elderly patients with severe chronic systolic HF of ischemic etiology [36].

Adiponectin

Among patients with ischemic heart disease, higher level of adiponectin was associated with HF and mortality [37]. Raised adiponectin level was related with worse baseline cardiac dysfunction. Adiponectin is useful in prognosis of HF but not MI.

Growth differentiation factor 15(GDF15)

Growth differentiation factor 15(GDF15)correlated with the etiology, severity and adverse cardiac events in HF. High concentration of GDF-15 corresponded with an elevated risk to develop HF in normal people from the society[38].

Mid-regional pro-A-type natriuretic peptide (MRproANP)

Mid-regional pro-A-type natriuretic peptide (MRproANP) surpassed BNP and NT-proBNP in the prediction of death in HF patients. New assay technology and high biological stability of MR-proANP could explain these facts [39]. MR-proANP is as useful as BNP for acute HF diagnosis in dyspneic patients and may provide extra clinical benefits when BNP is troublesome to interpret. MR-proADM distinguished patients with high 90-day mortality risk and adds prognostic value to BNP [40].

Pentraxin 3

Pentraxin 3 is an inflammatory marker which is significantly raised in HF with normal ejection fraction (HFNEF) and is independently associated with left ventricular failure due to diastolic dysfunction and HFNEF [41,42]. Pentraxin 3 is markedly high in HFNEF and is present in the coronary blood in diastolic dysfunction.

Insulin-like growth factor 1 (IGF-1)

Treatment with ACE inhibitors in an elderly population caused an increased in Insulin-like growth factor 1 (IGF-1) levels, especially in patients with subnormal cardiac function or ischemic heart disease [43]. High IGF1 levels correlated with high risk of cardiovascular mortality.

Albuminuria

Increased urinary albumin to creatinine ratio is a strong and independent predictor of prognosis in HF patient [44]. Microalbuminuria is an independent prognostic marker in patients with chronic HF. Patients with microalbuminuria had a tendency to have reduced left ventricular ejection fraction[45].

AMP-activated protein kinase (AMPK)

The cardio-protective effects of AMP-activated protein kinase (AMPK) activators are obtained on the long term by preventing or postponing the pathological phase from hypertrophy to HF. AMPK detects the energy state of the cell and sets up a general metabolic reaction to energy deprival. AMPK could be a potential target in HF development[46].

Soluble fms-like tyrosine kinase-1 (sFlt-1)

Soluble fms-like tyrosine kinase-1 (sFlt-1) is a tyrosine kinase protein that disables proteins which cause blood vessel growth. It was autonomously associated with degree of HF and may become a valuable tool in evaluating the effect of vascular remodeling on prognosis [47].

Conclusions

In the past five years, clinical usage of biomarkers in HF management has markedly increased worldwide. As we have seen in this review, several novel biomarkers have recently been validated and they will certainly be a plus for our physician in improving management and prognosis of HF. Some biomarkers like natriuretic peptides still have a major role to play in our clinical practice and sometimes combination of two biomarkers enhances prognosis. More studies involving cardiac biomarkers are needed to supervise treatment and this would most probably improve their clinical importance.

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