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Potential Biomarkers for Heart Failure Diagnostics and Management

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ABSTRACT

At the present time there is a progressive increase in the number of patients with chronic heart failure. Modern treatment is able to delay the progression of the pathological process in such patients, but not restore the normal physiology of the cardiovascular system. For these reasons, a need has emerged for a more detailed study of the biochemical and morphological processes leading to the development of chronic heart failure. This review discusses the potential of transforming growth factor-B1, cardiotrophin-1,Cystatin S andstimulating growth factor expressed by gene 2 (ST2) to become additional heart failure markers which will lead to the improvement of diagnostics and treatment of stable and decompensated heart failure.
MeSH words: chronic heart failure, transforming growth factor-B1, cardiotrophin-1,cystatin S, stimulating growth factor expressed by gene 2 (ST2).

INTRODUCTION

At the present time there is a progressive increase in the number of patients with chronic heart failure (CHF) [1, 2]. The widely used physical and instrumental methods allow to diagnose patients with objective symptoms of CHF. In such cases, modern treatment is able to delay the progression of the pathological process, but not restore the normal physiology of the cardiovascular system (CVS) [3]. For these reasons, a need has emerged for a more detailed study of the biochemical and morphological processes leading to the development of CHF. Determination of markers that allow to control the condition of risk group patients and prevent or delay the onset of heart failure will improve the prognosis of patients with cardiovascular diseases (CVD) and reduce mortality in this group[4,5,6].

In clinical practice, in the past decades the frequency of determination of N-terminal pro-brain natriuretic peptide (NT-proBNP) levels in blood serum has been increasing in patients with suspected acute heart failure or decompensation of CHF. This hormone is widely used in scientific studies of other biomarkers as a comparison standard due to the presence of a massive scientific data on its use.

NT-proBNP, just like brain natriuretic peptide (BNP), is synthesized and secreted mainly by the ventricles in response to myocardial wall distension, that is, to an increase in left ventricular (LV) filling pressure[7]. BNP and NT-proBNP have both natriuretic and antifibrotic effects [8]. Plasma BNP measurement is used to differentiate between HF and other diseases with severe dyspnea on admission to the emergency department[9,10].

Clinical guidelines indicate the appropriateness of determining BNP and NT-proBNP levels in patients with suspected HF, which will allow to limit the number of potential cases requiring echocardiography by excluding conditions with low levels of NT-proBNP, which indicates a non-cardiac nature of the pathology. However, the recommended exclusion thresholds differ across studies and clinical guidelines[11]. According to the current ESC guidelines for the HF management, the optimal cut-off value for NT-proBNP in acute HF or decompensated CHF is 300 pg / ml. For stable patients, the optimal exclusion threshold is 125 pg / ml for NT-proBNP [3]. In addition, it is important to keep in mind that the sensitivity and specificity of NT-proBNP determination for the diagnosis of CHF is lower in stable patients and there are no differences in its plasma concentration for patients with CHF of various etiologies.

In addition to what has already been said, it is extremely important to take into account the noncardiac factors that affect the level of NT-proBNP for the diagnosis of CHF[12]. Anemic syndrome is common in heart and renal failure and is one of the independent factors that influence the level of natriuretic peptides. For these reasons, NT-proBNP was found to be of diagnostic value in patients with CHF and preserved renal function. The level of NT-proBNP is also influenced by age, gender, body mass index (BMI), renal and liver function and diastolic blood pressure[13].

The described features of BNP and NT-proBNP levels assesment indicate that these hormones do not meet all the criteria for an ideal biomarker. The selection of additional biomarkers and the development of a multi-biomarker approach will be an important step towards improving the diagnosis and treatment of patients with stable and decompensated CHF.

Transforming growth factor-B1: An important pathogenetic link in the development of CHF is the structural remodeling of the myocardium, which occurs as a result of overloading the heart with volume or pressure, local ischemia, fibrosis and death of myocytes due to

apoptosis or necrosis. The development of adverse structural remodeling is mainly characterized by interactions between fibroblasts and paracrine signaling proteins, such as transforming growth factor-β1 (TGF-β1)[14]. TGF-β1 is one of three isoforms of the TGF-β superfamily. TGF-β1 is a major regulator of cardiac fibrosis. Changes in the structure of cardiac tissue, especially fibrous transformation, are considered the main cause of cardiac remodeling. The accumulation of the extracellular matrix increases the stiffness of the myocardium and, therefore, impairs the contractile properties of the heart muscle [15]. From the above, it follows that serum TGF-β1 may be a marker of chronic fibrous tissue transformation, but not a significant functional parameter of the left ventricle, such as NT-proBNP.

TGF-β1 is usually bound in a large latent complex with a half-life of about 90 minutes. Biological activity implies the release of TGF-β1 from the latent complex, which reduces the half-life to only 2 minutes [16].

The activation of TGF-β1 release from the inactive latent complex and the consumption of the active molecule by tissues in the context of cardiac fibrosis may explain the decrease in TGF- β1 serum levels in peripheral blood in patients with CHF. This idea is supported by experimental data showing that natriuretic peptides suppress adverse structural remodeling in the atria and ventricles. Atrial natriuretic peptide (ANP) and BNP inhibit collagen synthesis previously induced by angiotensin II, endothelin and specific fibroblast growth factors by affecting its mRNA level. In an experimental model with mice, ANP inhibited TGF-β1-induced transformation, proliferation, and collagen synthesis by myofibroblasts[17].

In their study, Behnes et al. evaluated serum TGF-β1 levels in 401 patients with atrial fibrillation (AF) and congestive CHF[15]. In patients with heart failure, the level of TGF-β1 was lower than in patients without it (p=0.0005). Similarly, in the study by Bielecka-Dabrowa et al. patients with hypertension and CHF had lower levels of TGF-β compared with patients who suffered from hypertension alone. This decrease might be the result of higher TGF-β1 consumption by the affected myocardium or due to the anti-fibrotic effect of natriuretic peptides. In addition to TGF-β1, this work evaluated the diagnostic efficacy of a number of other CHF biomarkers: Cystatin C (CysC), neutrophil gelatinase-associated lipocaine 2 (NGAL), galectin-3, type III collagen N-terminal propeptide (PIIINP), syndecan, tumor necrosis factor α (TNF-α), cardiotrophin 1 (CT -1), type I interleukin 1 receptor (IL1R1) and NT-proBNP. It was found that TGF-β is the only biomarker comparable in efficiency to NT-proBNP in this group[18].

Cardiotrophin-1: CT-1 is a recently identified member of the interleukin-6 (IL-6) family and one of the endogenous ligands of gp130 signaling pathways in the heart[19]. CT-1 causes hypertrophic growth and contractile dysfunction of cardiomyocytes. CT-1 level increases in various CVDs, including hypertension and CHF. Celik et al. found in their study that plasma CT-1 level was associated with diastolic CHF, calculated left ventricular filling pressure and positively correlated with NT-proBNP (p=0.001, r=0.349)[20].

Lopez et al. investigated the relationship between CT-1, left ventricular end-diastolic tension (LVEDP) and myocardial fibrosis in patients with hypertension and CHF. As a result, it was found that plasma CT-1 and NT-proBNP levels were increased (p <0.001) in patients with hypertension and CHF compared with the control group. In vitro, CT-1 stimulated the differentiation of human fibroblasts into myofibroblasts (p <0.05) and the expression of procollagen mRNA type I (p <0.05) and III (p <0.01) [21].

A meta-analysis by Song et al. included the results of 18 published studies evaluating the relationship between the level of CT-1 and CHF (n = 10), hypertension (n = 8), myocardial hypertrophy (n = 9). Serum CT-1 levels were significantly higher in patients with left ventricular hypertrophy (LVH) or CHF compared with controls. Subgroup analysis showed that CT-1 levels were highest in patients with CHF and LVH caused by hypertension, and slightly lower in patients with LVH caused by hypertension without CHF. It was concluded that increased plasma CT-1 values are associated with the risk of CHF in patients with hypertension. An excess of CT-1 indicates an increase in the amount of collagen in the myocardium in patients with hypertension and CHF. It is assumed that activation of CT-1 synthesis in cardiomyocytes in response to an increase in LVDV may contribute to fibrosis through stimulation of fibroblasts in CHF caused by hypertension. Therefore, CT-1 can serve as a new biomarker for monitoring the condition and effectiveness of treatment in patients with hypertension[19].

Cystatin S: CysC is a small, low weight molecular protein from the group of cysteine proteinase inhibitors. It is produced by all nucleated cells in the body and secreted into the extracellular space at a constant rate. With its low molecular weight and isoelectric point at pH=9.3, it is easily filtrated in kidneys. In the proximal tubules, it is absorbed and then catabolized and therefore does not return to the bloodstream[12]. CysC is not excreted in urine, so the clearance of CysC cannot be determined, while its plasma concentration correlates with the glomerular filtration rate (GFR). Plasma CysC measurement has several advantages over other markers clinically used to assess GFR. It is more accurate than plasma creatinine clearance or Cockcroft-Gault creatinine clearance and more reliable than 24-hour creatinine clearance[23].

Renal dysfunction/failure is an independent marker of LVH and a reliable predictor of morbidity and mortality in CVD. In patients with chronic kidney disease, there is a significant association between decreased GFR and the development of LVH. Renal failure is an indicator of the heart failure severity and contributes to its progression[24].

Left ventricular hypertrophy is an important form of target organ damage in hypertension and an independent risk factor for cardiac death, arrhythmias, and CHF. In a study by Li et al., a positive correlation was found between serum CysC levels and interventricular septal thickness, posterior wall thickness and left ventricular mass index, and serum CysC was an independent marker of LVH induced by hypertension[25].

Elevated CysC level is an independent risk factor for increased mortality in elderly patients with CHF[23].

In a study by Manzano-Fernandez et al., the authors added CysC, creatinine, and the MDRD formula to cardiac biomarkers in order to increase effectiveness in stratifying the risk of a large cohort of patients with acute heart failure.

The highest CysC-tertile (> 1.50 mg / L) was a significant independent risk factor for adverse events (hazard ratio (RR) 3.08, 95% CI 1.54-6.14, p=0.004) in contrast to creatinine and MDRD formula. A multimarker approach combining cardiac troponin T, NT-proBNP, and CysC further improved risk stratification, showing that patients with two (RR 2.37, 95% CI (1.10-5.71)) or three (RR 3.64, 95% CI (1.55–8.56)) elevated biomarkers had a higher risk of developing adverse cardiovascular events than patients without elevated biomarkers (p = 0.015)[26].

Moran et al. examined 4453 patients aged 65 years and older with no heart failure at the start of the Cardiovascular Health Study to analyze the relationship of CysC with the risk of HF with preserved ejection fraction (HFpEF) and the risk of HF with reduced ejection fraction (HFrEF). Over eight years of follow-up, 167 patients developed HFpEF and 206 patients developed HFrEF; an increased risk of HFpEF was found only in the highest quartile of CysC (RR 2.25; 95% CI (1.33–3.80), while a linear trend was present for HFrEF[27].

Serum CysC is a novel stable biomarker that is unaffected by gender, age, exercise, diet, BMI, muscle mass, or serum creatinine. The increased predictive power provided by the multi-biomarker panel can help to identify with higher accuracy high-risk patients whosetreatment can be altered for achieving better results.

Stimulating growth factor expressed by gene 2 (ST2): ST2 is a member of the IL-1 superfamily, which is involved in inflammatory processes, especially in relation to mast cells, CD4 + T-helper type 2, and the production of TH2-associated cytokines [28]. There are two known isoforms of this growth factor: transmembrane (ST2L) and soluble (sST2). Excessive levels of sST2 in the bloodstream also function as a decoy receptor for IL-33, preventing its beneficial anti-necrotic and anti-remodeling effects, which ultimately leads to cardiac fibrosis and ventricular dysfunction[29]. In addition, it was found that under mechanical stress of cultured cardiomyocytes, the ST2 gene undergoes pronounced activation[30]. However, the relative contribution of ST2 to each of the aforementioned pathways and the pathogenetic link in which its predictive value is influenced by varying degrees of inflammation, necrosis, myocardial remodeling, or deformity are unknown.

The possibility of using ST2 as a universal biomarker for determining CHF were studied by Bayesgenis et al. They evaluated the levels of ST2, NT-proBNP, high-sensitivity C-reactive protein (hsCRP) (a marker of inflammation), as well as galectin-3 and high-sensitivity cardiac troponin T (hsTnT) (biomarkers of necrosis and remodeling) in 1015 patients with CHF. The sST2 concentrations showed a statistically significant, but weak correlation with the biomarkers used for stress, inflammation and myocardial fibrosis. ST2 correlated most strongly with NT-proBNP (r = 0.32; P <0.001), to a lesser extent with hsCRP and hsTnT (r = 0.30; P <0.001 for both) and only slightly with galectin-3 (r = 0.15; P <0.001). After adjusting for age, sex, and estimated glomerular filtration rate, the ST2 correlation did not significantly change with any biomarker (data not shown). Importantly, soluble ST2 remained a significant and independent predictor of risk, regardless of NT-proBNP, hsCRP, galectin-3, and hsTnT concentrations even after adjusting for age, sex, LVEF, NYHA functional class, ischemic etiology of CHF, and estimated glomerular filtration rate[31].

Wang et al. evaluated the possibilities of sST2 clinical use in patients with stable HFpEF in comparison with NT-proBNP. The results showed that the patients with HFpEFhad higher serum NT-proBNP and sST2 levels than the control group. However, it was not possible to differentiate patients by functional classes of CHF using ST2 alone. The main conclusion of this study was that serum sST2 can provide diagnostic information about stable HFpEF in patients with hypertension, and NT-proBNP can provide additional insight into the FC of CHF and the severity of diastolic dysfunction[32].

CONCLUSION

Based on modern research, new biologically active substances that can be used as biomarkers in patients with chronic heart failurehave become known. They are sensitive to various pathological processes in the myocardium, therefore, they are able to complement each other and be used individually in certain groups of patients. Further study of biomarkers and the development of algorithms for their use in patients with chronic heart failure of various etiologies and risk groups will enhance stability control and postpone unfavorable outcomes.

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