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Diagnostic and Prognostic Biomarkers of Heart Failure: The Impacts, Implementation and Future Outcomes

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Review Article

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ABSTRACT

Heart failure (HF) is a major leading cause of mortality and morbidity worldwide. The primary and secondary preventions of chronic heart failure are a priority for the health system and require multiple approaches to increase their effectiveness. Serum Cardiac Biomarkers are tools used to more accurately identify high-risk individuals of chronic Heart Failure, to speed the diagnosis, and to aid in treatment and prognosis determination. This review aims to highlight the importance of utilization of a variety of these cardiac biomarkers in assessment of asymptomatic HF patients, and decompensated symptomatic cases of chronic heart failure and to raise relevant points of their clinical use and the promises for the coming years for better management under different types of pharmacotherapeutic lines for treatment of chronic heart failure.

INTRODUCTION

Chronic Heart Failure (CHF) is a pathophysiological condition; in which the heart is unable to pump sufficient amounts of blood to satisfy the metabolic needs of the tissues and organs of the body. CHF is a complex syndrome elicited by various pathological diseases such as ischemic heart disease, hypertension, valve disease, myocarditis, autoimmunity, toxins, different cardiomyopathies, but coronary artery disease is the most common etiology of the HF in industrialized nature. Furthermore, CHF is a major health problem in western countries especially the united stated; that leads to a considerable high morbidity and mortality due to increased risk of developing ventricular arrhythmias and sudden death.

Pathophysiology of chronic heart failure

Heart Failure is associated with a variety of pathophysiological changes that trigger the progress of this disease. The development of pathological ventricular remodelling is mediated by neurohormonal activation and the synthesis of proinflammatory cytokines; such as tumor necrosis factor-α (TNF-α) that appears to play the predominant role and the elevated levels of this biomarker are correlated with reduced peripheral blood flow, apoptosis and smaller skeletal muscle mass. In addition to this, proinflammatory cytokine biomarker levels are

correlated with the prognosis of HF; where higher plasma levels of TNF-α and high sensitive C-reactive protein (hs-CRP) biomarkers are associated with weight loss and cardiac cachexia, a serious complication of HF with increased mortality [1].

The Renin-Angiotensin System (RAS) is known to play a dominant role in the pathophysiology of CHF; where some evidences from clinical and experimental studies indicate that RAS are linked in the pathophysiology of cardiac hypertrophy, apoptosis and remodeling. They suggested that a relationship exists between the RAS and immune activation in heart failure. Furthermore, CHF is associated with endothelial dysfunction, where the activation of the RAS is believed to be important in the deterioration of endothelial dysfunction in CHF through stimulation of oxidative stress, and this endothelial dysfunction leading to abnormal vasomotor control may give rise to increased peripheral vascular resistance, a hallmark of CHF [2]. So, the prevention or reversal of the endothelial dysfunction may be considered an important target for pharmacological intervention in CH. It is well accepted that CHF is associated with over sympathetic activity and impaired arterial baroreflex function. Thus, this excessive sympathetic activation not only exacerbates the HF state but also is prognostic of complications and death; therefore, it has been considered a prime therapeutic target in the treatment of CHF to reduce excessive sympathetic activation.

Mediators playing a role in pathogenesis of heart failure

Proinflammatory cytokines biomarkers are important mediators for the development of HF. These cytokines can damage cardiomyocytes and/or endothelial cells which play a pivotal role in the pathogenesis and progress of CHF. Where it was reported that TNF-α is a proinflammtory cytokine, exerted a negative inotropic effect on the heart with more cardiac cachexia, anemia and activation of RAS. It is produced in a variety of conditions such as acute myocarditis, reperfusion injury and CHF; increasing the severity of CHF.

C-reactive protein (CRP) is a protein that increased highly in patient of CHF, and was associated with high morbidity and mortality, as it causes plaque instability, induces adhesion molecule expression, and associates with endothelial dysfunction, that all promoting cardiac inflammation and aggravation of heart failure.

Nitric oxide (NO) is a free radical that is known to be an important determinant of vascular tone. In the heart apart from controlling coronary blood flow, NO may also affect cardiac function. It was found that cytokines as TNF-α stimulates the enzyme inducible nitric oxide synthase, NO, and its product upon reaction with superoxide anion, peroxynitrite, being an important source of free radical stress in cardiac and vascular tissue. It is also clear that the biological activity of NO is altered during heart failure.

The receptor Fas (APOI/CD95) is a type 1-transmembranous glycoprotein and is a member of the tumor necrosis factor receptor superfamily that mediate apoptosis and in addition to this, hypoxia is frequently seen in advanced CHF can stimulate Fas to induce apoptosis in the heart myocytes; that playing a role in the pathophysiologic mechanisms of CHF. Moreover a study reported that elevated levels of serum IL-2R, TNF-α, NO, sFas and ACE were significantly elevated in patients with congestive heart failure regardless the etiology of HF.

Cardiac remodeling and cardiac biomarkers release

Cardiac remodeling is defined as a genomic expression that results in molecular, cellular and interstitial changes in the heart leading to releasing some diagnostic and prognostic biomarkers. Remodeling is associated with myocyte hypertrophy, myocyte loss from necrosis or apoptosis, as well as interstitial cell growth, especially fibroblast proliferation, leading to myocardial fibrosis. Moreover, cardiac remodeling is influenced by hemodynamic load, neurohumoral activation, and other factors that further adversely affect the remodeling process.

As heart disease progresses towards CHF, the myocardium undergoes profound alterations in its structure and function at several levels. As the size of the organ increases and function deteriorates, there is gradual transformation from a compensated to a decompensated condition during which clinical symptoms of CHF become visible (dyspnea, peripheral edema, increased heart rate, decrease in physical activity). The complex process responsible for this gradual deterioration leading to development of mechanical (pump failure) and electrophysiological dysfunction (arrhythmias) is called pathologic cardiac remodeling with a variety numbers of biomarkers in the serum, and with development of important clinical consequences, such as decreased quality of life and premature death Thus, to improve symptoms and increase survival in patients with CHF, it is very important to detect these biomarker early to find ways to reduce and prevent ventricular remodeling.

Biomarkers in heart failure

An increasing number of blood enzymes, hormones, biologic substances, and other markers of cardiac stress and malfunction, as well as myocyte injury, collectively referred to as cardiac biomarkers of HF, that appear to have growing clinical importance and impacts on progress of HF. These biomarkers have expanded their role from merely being adjunctive, such as in the case of cardiac necrosis confirmation, to become the gold diagnostic standard and strong prognostic measures in a variety of cardiac diseases, especially CHF [3]. The ideal biomarker of heart failure should be characterized by its high sensitivity, specificity, reproducibility, widely available, and cost-effective. Therefore, the search for an ideal biomarker in CHF is still ongoing, with several newly discovered biomarkers of heart failure.

DISCUSSION

Biomarkers of myocyte stress in heart failure (Natriuretic Peptides)

The precursor of BNP and N-terminal pro–brain natriuretic peptide (NT-pro-BNP) is a pre–prohormone BNP, a 134-amino-acid peptide that is synthesized in the myocytes and cleaved to the prohormone BNP of 108 amino acids. The prohormone is released during hemodynamic stress, that is, when the ventricles are dilated, hypertrophic, or subject to increased wall tension. Prohormone BNP is cleaved by a circulating endoprotease, termed corin, into two polypeptides: the inactive NT-pro-BNP, 76 amino acids in length, and brain natriuretic peptide (BNP), a bioactive peptide 32 amino acids in length. BNP causes arterial vasodilation, diuresis, and natriuresis, and reduces the activities of the renin–angiotensin–aldosterone system and the sympathetic nervous system. Thus, when considered together, the actions of BNP oppose the physiological abnormalities in heart failure.

Some clinical studies reported that, measurements of BNP appear to be useful in the diagnosis and risk stratification of patients with chronic heart failure and also, useful in screening asymptomatic subjects at risk of developing heart failure, such as the elderly and those with hypertension, diabetes, or asymptomatic coronary artery disease [4]. Also, BNP measurements are a better predictor of death than plasma norepinephrine or endothelin-1. However, there were several studies reported that, there was a moderate increase in the level of circulating BNP with increasing age, presumably in relation to myocardial fibrosis or renal dysfunction, which are common in the elderly, and also, the BNP level varied inversely with the body-mass index, and in addition to this, pulmonary hypertension from a variety of causes may increase the plasma level of BNP. Additionally, natriuretic peptides are still failing to comply with all the properties of an ideal biomarker.

New developing biomarkers in heart failure

These new biomarkers are still under investigation. They include chromogranin A, a polypeptide hormone produced by the myocardium, which has potent negative inotropic properties and elevated plasma levels in patients with heart failure [5]. A second new biomarker is galectin-3, a protein produced by activated macrophages, for which plasma levels have been reported to predict adverse outcomes in patients with heart failure. A third new biomarker is osteoprotegerin, a member of the tumor necrosis factor receptor superfamily that has been implicated in the development of left ventricular dysfunction, and in predicting survival in patients with heart failure after myocardial infarction.

Implementation and utilization of cardiac biomarkers

A biochemical cardiac marker to be considered useful in guiding the management of patients with heart failure. Single biomarker to track all of the different pharmacotherapeutic measures is not satisfactory ; so, use of Plasma natriuretic peptides, including Atrial Natriuretic Peptide (ANP) and BNP plus both cardiac troponins and C-reactive protein are increasingly being recognized as important prognostic markers in patients with heart failure; for assessing the effectiveness of heart failure therapy. In the near future, there is great enthusiasm for such a multimarker approach as many of these biomarkers will provide important new insights into pathophysiology and aid in the diagnosis and management of HF patients and for providing large numbers of values quickly and cheaply.

CONCLUSION

Different cardiac biomarkers are central to the diagnosis and risk stratification of HF and also, these biomarkers are used to monitor drug therapies. Although older biomarkers are well established, newer biomarkers are offering the possibility of further risk stratification, quantification of the severity of heart failure stage, and even marking the correction of cardiac dysfunction by demonstrating the reappearance of normal physiology of heart.

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