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REVIEW PAPER

The role of biomarkers of stress in heart failure

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Abstract

According to the literature, there are numerous stress biomarkers. However, for the first time, this review article summarizes the role of major physiological stress biomarkers in heart failure collectively which include chromogranin A, catecholamines, copeptin, cortisol, liver-type fatty acid-binding protein (L-FABP), superoxide dismutase (SOD) and catalase, fibrinogen, malondialdehyde, heat shock proteins. Chromogranin A (CgA) serum levels are increased in patients with chronic heart failure and are a predictive factor for mortality. A novel mechanistic insight for elevated catecholamine levels in plasma commonly seen in chronic heart failure (HF) conditions, suggests that increased trans-synaptic activation of the chromaffin cells within the adrenal medulla may increase catecholamines in the circulation and, in turn, contribute to the enhanced neurohumoral drive. Elevated copeptin plasma concentrations seen in HF patients were linked to an increased risk of all-cause death suggesting that copeptin may function as an HF

outcome predictor. Since cortisol is a general stress indicator, serum cortisol levels in congestive heart failure (CHF) may reflect worse hemodynamic parameters and systemic sympathetic nerve activity. In individuals with acute heart failure, an elevated urine L-FABP level before therapy may indicate worsening renal function. Compared to children without heart failure, children with heart failure have decreased levels of SOD. In contrast to children without heart disease, children with heart failure had greater catalase (CAT) levels. In children with left-to-right shunt congenital heart disease (CHD), oxidative stress was the primary factor contributing to the development of heart failure. The individuals with acute aggravation of chronic heart failure who have high fibrinogen levels ($\geq$ 284 mg/dL) were independently predicted to die. Malondialdehyde is a sign of lipid peroxidation which was detected in the plasma of congestive heart failure patients with varied levels of clinical symptoms and in healthy individuals. HSPs can reduce heart dysfunction in HF and carry out a variety of additional functions, including regulating apoptosis and possessing anti-oxidant and anti-inflammatory properties.

Keywords: biomarkers, stress, heart failure, pathogenesis

Introduction

Heart failure (HF) is a complex, fatal disease with high expenses, major morbidity and mortality, poor functional ability, and quality of life. Almost 64 million individuals worldwide have HF [1]. Heart failure is a group of heart conditions that affect the myocardium's ability to contract which including hypertension, coronary artery disease, diseases of the heart valves, myocarditis, and cardiomyopathy [2–4]. On the other hand, stress is an inevitable response in all organisms at the molecular to the whole-body level to maintain their homeostasis. The quantitative and qualitative assessment of biomarkers allows for the monitoring of stress levels such as acute phase proteins, heat shock proteins, innate immune indicators, oxidative stress markers, chemical discharges in saliva and urine, and oxidative stress were all examples of potential stress markers. The prognosis of stress-related illnesses and disorders, as well as the direction of therapy, are all important aspects of how stress biomarkers are used [5].

Major cardiovascular risk factors include hypertension. Vascular damage caused on by oxidative stress (excess bioavailability of reactive oxygen species [ROS]), one of the several mechanisms involved in the pathophysiology of hypertension, was particularly significant. ROS physiologically control the function of the vasculature via redox-sensitive signalling pathways. Oxidative stress encourages vascular remodelling, inflammation, and endothelial dysfunction in hypertension, which results in vascular damage. The main cause of vascular ROS is nicotinamide adenine dinucleotide phosphate oxidases, which are the focus of several therapeutic research efforts [6]. Noushad et al. explained the potential diagnostic biomarkers of chronic stress such as cortisol, adrenocorticotropic hormone, catecholamines, glucose, HbA1c, triglycerides, cholesterol, prolactin, oxytocin, dehydroepiandrosterone sulfate, C-reactive protein (CRP), fibrinogen and interleukin-6 and 8, and more [7]. In the same way, Dhama et al. — copeptin, chromogranin A, heat shock proteins, Liver-type fatty acid-binding protein, endothelin-2, malondialdehyde, SOD and catalase, blood urea nitrogen and creatinine, acute phase proteins and more [5].

According to the literature, there are numerous stress biomarkers [5, 7]. However, for the first time, this review article summarizes the role of major physiological stress biomarkers in the pathogenesis of heart failure collectively which include chromogranin A (CgA), catecholamines, copeptin, cortisol, liver-type fatty acid-binding protein (L-FABP), SOD and catalase, fibrinogen, malondialdehyde (MDA), heat shock proteins (HSPs).

Science Direct, PubMed, and Google Scholar were only a few of the databases used to review the literature. February 15, 2023, was the last date of the literature search. Keywords such as “biomarkers,” “stress,” “heart failure,” and “pathogenesis” were used. Clinical investigations could only be conducted in English. While we did focus more on current studies, we did not impose a time constraint. It was possible to find related articles by looking through the references of the relevant papers.

The role of stress biomarkers in heart failure

There are numerous stress biomarkers but this article only focuses the role of chromogranin A, catecholamines, copeptin, cortisol, L-FABP, SOD and catalase, fibrinogen, MDA, and HSPs in the pathogenesis of heart failure as explained in figure 1 and 2.

Chromogranin A

A prohormone called chromogranin A (CgA) is generated by a variety of tissues, including the cardiac, neuroendocrine, and endocrine tissues. The amount of CgA has a strong correlation with sympathetic activity in the peripheral nervous system and adrenal gland, which increases the possibility that it might be used as a marker for sympathetic activity in people. As a biomarker for neuroendocrine tumors, it has also been studied in the past [8, 9].

The secretory granules of neuroendocrine cells include the acidic protein chromogranin A. The neuroendocrine tumor marker CgA is present in plasma. CgA measurement has attracted attention in cardiovascular illness because higher plasma concentrations are linked to a higher risk of clinical deterioration and mortality in individuals with acute coronary syndromes or chronic heart failure [10].

Numerous hormonal systems are active in chronic heart failure, which has consequences for diagnosis and prognosis. Ceconi et al. investigated the theories that serum CgA which is a protein of 49 kDa acid found in the secretor granules of neuroendocrine cells, was elevated in chronic heart failure and that CgA levels were a marker for mortality. A pro-hormone called CgA was the beginning of various biologically active components that may have an impact on chronic heart failure. Patients with chronic heart failure had higher levels of CgA serum, which was a predictor of death [11].

Previous studies have shown that CgA levels can predict mortality in heart failure, but there was presently little information on how CgA was processed in HF or if the CgA fragment catestatin (CST) may have a direct impact on cardiomyocyte function. In contrast to CST alone, the authors discovered the CgA-to-CST ratio to be an important predictive biomarker in acute HF. Furthermore, it showed increased cardiac CgA glycosylation and poorer CgA processing in HF, which should be viewed negatively because CST decreases diastolic Ca^{2+} leak via direct CaMKIIδ inhibition. As a result, even while CgA production appears to increase and likely

serves as a counter-regulatory mechanism in HF, this system may not work properly due to increased myocardial CgA glycosylation [12].

Similarly, CgA predictive power was equivalent to that of N-terminal pro-BNP (NT-proBNP) in acute heart failure. In these cases, the combination of CgA and NT-proBNP could enhance prognosis prediction [13]. Elderly people still have difficulty being assessed for cardiovascular risk. The authors investigated the potential use of plasma CgA measurement in predicting mortality risk in elderly heart failure patients receiving primary medical treatment. Elderly patients with heart failure symptoms can be identified as having a higher risk of short- and long-term death by measuring the concentration of CgA in their plasma [10]. In contrast, another study concluded that circulating CgA level measurements in people with chronic, stable heart failure wouldn't add any predictive information to what can be learned from a physical exam, normal biochemical testing, and contemporary HF biomarkers [14].

Catecholamines

The primary neurotransmitters that mediate several central nervous system processes, including motor control, cognition, emotion, memory processing, and endocrine regulation, are catecholamines, which include dopamine and norepinephrine. Several neurologic and neuropsychiatric illnesses are linked to dysfunctions in catecholamine neurotransmission [15]. A novel mechanistic insight for elevated catecholamine levels in plasma commonly seen in chronic HF conditions, suggests that increased trans-synaptic activation of the chromaffin cells within the adrenal medulla may increase catecholamines in the circulation and, in turn, contribute to the enhanced neurohumoral drive [16].

Congestive heart failure is considered harmful by those who are stimulated by catecholamines. It has been hypothesized that catecholamine administration was linked to altered myocardial energetics in CHF and that myocardial O_2 needs associated with catecholamine stimulation in CHF were excessive [17–19]. Moreover, before coronary angiography is possible in patients with life-threatening acute HF, echocardiography, including speckle-tracking-derived echocardiography (STE), can identify a highly probable acute phase of Takotsubo syndrome (TTS). In such patients, if necessary, any catecholamine administration should be continuously

monitored by echocardiography and stopped as soon as the signs of TTS become more obvious [20].

Copeptin

Copeptin is produced with vasopressin (VP) and then released in equimolar levels. Its stability and longer half-life than VP are reasons why it is used as a surrogate biomarker for VP. It is shown that plasma VP levels and plasma copeptin have a good correlation [21, 22]. In the same way, amrousy et al. examined the capacity of copeptin level to predict unfavourable outcomes in paediatric heart failure and copeptin level was associated with different clinical and echocardiographic data. Plasma copeptin level was significantly higher in the patient group (16.2 ± 5) pmol/L compared to the control group (4.1 ± 2.3) pmol/L, $p < 0.001$. For predicting worse outcomes in paediatric heart failure, plasma copeptin level has a strong predictive value. Additionally, copeptin and the severity of paediatric HF were closely correlated [23].

Copeptin was higher in the current heart failure with preserved ejection fraction (HFPEF) patients and was correlated with NT-proBNP but not with indicators of diastolic dysfunction, and has prognostic consequences; however, these effects were blunted once NT-proBNP was taken into account. In contrast to diastolic dysfunction, neurohormonal activation indicators may provide a more accurate representation of the pathophysiology of HFPEF [24]. Likewise, the current meta-analysis shows that elevated copeptin plasma concentrations seen in HF patients were linked to an increased risk of all-cause death suggesting that copeptin may function as an HF outcome predictor [25].

In patients with acute myocardial infarction (AMI) who have heart failure, copeptin is a potent and unique predictor for mortality and morbidity. Copeptin outperformed B-type natriuretic peptide (BNP) and N-terminal pro-BNP (NT-proBNP) in the group in terms of its predictive power. Copeptin may help further enhance risk assessment in patients with chronic heart failure and more precisely characterize the patient group at higher risk if the results of this study were supported by more research [26].

According to Xu et al. heart failure with reduced ejection fraction (HFrEF) in patients who were exacerbating it increases plasma copeptin levels. In the course of progression in HFrEF patients,

copeptin was implicated. Since HFrEF may be predicted and evaluated in the clinic, the copeptin value may be useful [27]. In the same context, Maisel et al. explained individuals with elevated copeptin, particularly those with hyponatremia, had significantly higher 90-day mortality, readmission rates, and electrocardiographic (ER) visits. Copeptin significantly improved the predictive value of clinical predictors, serum sodium, and natriuretic peptides in patients with acute HF. Copeptin was highly prognostic for 90-day adverse events [28].

Copeptin levels in children with HF due to cardiomyopathies have never been reported before in research. Children with HF with cardiomyopathies have higher copeptin levels. It was significantly correlated with the B-type natriuretic peptide (BNP) level, somewhat with the clinical HF and left atrial volume grading, and weakly with the left ventricular ejection fraction (LVEF) [29]. Independent of clinical factors, plasma sodium, and dosages of loop diuretics, plasma copeptin levels in outpatients with chronic heart failure predict death. Additionally, copeptin predicts the combined endpoint of hospitalization or death apart from NT-proBNP [30].

Left ventricular dysfunction (LV dysfunction) and clinical heart failure are both a result of acute myocardial infarction (AMI). Heart failure is connected with an increase in arginine vasopressin, and worse outcomes following an AMI are linked to pro vasopressin's C-terminal (copeptin). Kelly et al. investigated the relationship between copeptin and clinical heart failure following an AMI, as well as its relationships with LV dysfunction, volumes, and remodelling. Clinical cardiac failure following an AMI was linked to copeptin along with LV dysfunction, remodelling, and volume. Arginine vasopressin (AVP) system failure following a myocardial infarction (MI) might be treated by targeting copeptin measurements, which may also give prognostic information [31].

A common condition with a poor prognosis, heart failure (HF) is becoming more prevalent. Copeptin, a vasopressin (VP) marker, can predict the onset of diabetes mellitus, diabetic heart disease, coronary artery disease, and early death. Copeptin was increased in HF patients and indicates a worse outcome. Independent of the presence of diabetes or traditional cardiovascular risk factors, copeptin can predict the onset of HF in older persons. The authors suggested that copeptin has the potential to be employed as a risk marker for incident HF and that an overactive VP system calls for more research in the development of HF. It is rather easy to use and use biomarkers as risk indicators in risk ratings. Future research has an intriguing

potential to be helpful in clinical practice if it can demonstrate that adding copeptin to HF risk ratings heightens their predictive ability [32].

Heart failure has as a fundamental characteristic increased neurohormonal activity. Copeptin is a surrogate for proarginine vasopressin, and copeptin has been shown to have predictive significance for several disease conditions with both nonvascular and cardiovascular pathophysiology. Increased mortality and hospitalization risk, as well as a correlation with the severity of HF, have all been linked to elevated plasma copeptin in HF patients [33].

The severity of heart disease has also been linked to vasopressin. A previously unevidenced topic in the field of heart failure is copeptin, an inactive component of the vasopressin precursor. For patients with severe HF, Stoiser et al. demonstrated that copeptin was an outstanding outcome predictor. BNP was still a good predictor of re-hospitalization for chronic heart failure, but its value was greater than that of BNP in predicting mortality and a combined endpoint. The authors' findings suggest that a novel focus for the population's treatment might be vasopressin antagonistic effects [34].

B-type natriuretic peptide (BNP) is considered an established prognostic marker for heart failure patients. Gegenhuber et al. provided evidence that mid-regional pro-A-type natriuretic peptide (MR-proANP), mid-regional pro-adrenomedullin (MR-proADM), and the C-terminal part of the arginine vasopressin prohormone (copeptin) measurements might have similar predictive properties compared with BNP determinations for one-year all-cause mortality in acute destabilized heart failure [35].

Cortisol

The main stress hormone is cortisol which is increased in response to stress by the hypothalamic-pituitary-adrenal (HPA) axis [36]. Numerous physiological reactions are triggered by elevated cortisol, including the mobilization of energy (by boosting blood glucose, which is followed by the breakdown of proteins and lipids) and the maintenance of homeostasis (via inducing vasoconstriction and sodium retention) [37]. Since cortisol is a general stress indicator, serum cortisol levels in congestive heart failure (CHF) may reflect worse hemodynamic parameters and systemic sympathetic nerve activity. It might be the serum cortisol levels were positively

correlated with pulmonary capillary wedge pressure and norepinephrine (NE) and negatively correlated with left ventricular ejection fraction and cardiac index [38].

Cortisol levels have been demonstrated to increase morbidity and mortality in chronic heart failure. In individuals with chronic heart failure, a high blood cortisol level is an independent predictor of the risk of early cause mortality. High levels of cortisone for the first 48 hours were one of the factors that predict mortality, and high cortisol levels predict early mortality. Given these results, it was supposed that careful monitoring of these markers which might be easily followed in clinical settings, may assist the clinician in more accurately predicting mortality [39].

High levels of circulating aldosterone are linked to a poor prognosis in individuals with systolic heart failure, while mineralocorticoid receptor blocking increases survival. In chronic heart failure, cortisol may also bind to and activate the mineralocorticoid receptor, but its prognostic importance was uncertain. Higher blood levels of both cortisol and aldosterone were independent predictors of increased mortality risk in individuals with chronic heart failure, providing complementary and additional prognostic value [40].

Liver-type fatty acid-binding protein (L-FABP)

L-FABP, a naturally occurring antioxidant protein produced in proximal tubular epithelial cells which is secreted into the tubular lumen as a consequence of ischaemia or oxidative stress [41]. Likewise, Sunayama et al. showed that urinary L-FABP, a new tubular marker, may offer predictive information in patients with acute heart failure that might not be possible to get using established prognostic variables and tubular markers. It would be wise to conduct more research to see how this link could be therapeutic [42]. In individuals with acute heart failure, an elevated urine L-FABP level before therapy may indicate worsening renal function (WRF). Because it can anticipate negative effects, more research was necessary [43].

In patients with acute decompensated heart failure, urinary L-FABP levels help predict the beginning of acute kidney damage. These findings may aid in the early diagnosis of acute kidney damage in patients with acute decompensated heart failure, which might lead to advancements in the care of the patient population [44].

SOD and catalase

Reactive oxygen species (ROS) may have a role in deleterious myocardial remodelling and the development to failure, according to a number of lines of evidence [45, 46]. Heart failure, is the most frequent consequence of acyanotic congenital heart disease (CHD), there was yet no adequate definite diagnosis or treatment. The development of heart failure is frequently linked to the process of oxidative stress. The initial line of antioxidant defense against superoxide anion is superoxide dismutase (SOD). While catalase (CAT) enhances earlier detoxification by SOD by dissolving hydrogen peroxide into water and oxygen molecules. In a left to right shunt acyanotic CHD, those with heart failure and those without it had significantly different levels of SOD and CAT. Compared to children without heart failure, children with heart failure have decreased levels of SOD. In contrast to children without heart disease, children with heart failure had greater CAT levels. In children with left-to-right shunt CHD, oxidative stress was the primary factor contributing to the development of heart failure [47].

Qin et al. concluded that myocyte-specific production of catalase slows the progression of left ventricular (LV) remodelling and the emergence of overt heart failure while having no effect on the initial aberrant myocardial phenotype in Gαq mice. Catalase has a positive impact by significantly inhibiting interstitial fibrosis, myocyte death, and myocyte hypertrophy. These findings answer a number of fundamental, unanswered queries about the function of ROS in cardiac failure [48].

Fibrinogen

Heart failure is a prevalent cardiovascular condition that has long been linked to systemic inflammation. Fibrinogen (FIB) is a marker for thrombosis and inflammation that is connected to the prognosis of many disorders. However, it is unknown how fibrinogen level affects the prognosis of critically sick individuals with abrupt aggravation of chronic heart failure. According to Meng et al. individuals with acute aggravation of chronic heart failure who have high fibrinogen levels (≥ 284 mg/dL) were independently predicted to die. The authors have suggested for the need of larger prospective studies with longer follow-up periods to further

confirm the findings [49]. Also, Chin et al. concluded that IL-6 and tissue factor (but not VEGF, plasma viscosity, vWf, fibrinogen or soluble P-selectin) levels were predictors of mortality and poor prognosis in congestive heart failure CHF [50].

Malondialdehyde

Malondialdehyde (MDA) is a sign of lipid peroxidation which was detected in the plasma of congestive heart failure patients with varied levels of clinical symptoms and in healthy individuals. Mean MDA concentrations in groups A (2.65 ± 1.03 μmol/L) and B (2.1 ± 0.7 μmol/L) were significantly higher than those in the control group (1.45 ± 0.77 μmol/L; $p < 0.05$), supporting the hypothesis that the CHF state and underlying risk conditions appear to be associated with abnormal oxidative stress. Moreover, a significant correlation was found in group A patients between the MDA values and the duration in years (chronicity) of the CHF state [51].

Another study examined a variety of oxidative stress indicators and how they affected mortality and morbidity in HF patients. Finally, even after correcting for a wide range of other indicators, including well-known NT-proBNP, malondialdehyde and uric acid (UA) were significantly linked to a poorer prognosis in the group of patients. One-year all-cause mortality may benefit from the proposed biomarkers. Noninvasive laboratory testing, such as MDA and UA tests, are routinely accessible. According to the study's findings, it was confirming increased MDA and UA levels as independent indicators of outcome has potential significance for risk classification of patients with chronic heart failure. The therapeutic applicability of the aforementioned findings, however, has to be confirmed in further research [52].

Heat shock proteins (HSPs)

Heat-shock proteins (HSPs) are induced, in part, by denatured proteins produced during heat shock, ischemia and other stresses [53]. For people at risk for cardiovascular disease, HF is among the most important causes of morbidity and death. The development of cardiac hypertrophy and fibrosis which are linked to the emergence of heart dysfunction which is known

to be significantly triggered by extracellular HSP70. HSP70 may have a role in the HF response, although it is yet unclear if HF treatments might use it as a target. Liu et al. highlighted a novel role for extracellular HSP70 in promoting HF via activation of toll-like receptor 2-p38-NF-κB–mediated noninfectious inflammatory response in myocardium, which suggests a possible therapeutic approach against HF by blocking the biological functions of extracellular HSP70 or its receptor, toll-like receptor 2 (TLR2) [54].

Important new approaches for the diagnosis, prognosis, and perhaps treatment of heart failure is being revealed by accumulating evidence for the roles of extracellular HSP70, HSP90, and BAG-3 in mechanistically controlling the pathophysiology of disease. Given the wide range of factors contributing to protein misfolding and proteinopathies (including those brought on by mutations) in heart failure, it will be important to better understand how intracellular and extracellular HSPs mediate disease in order to optimize therapies for particular diseases and stages [55].

HF is the advanced stage of a number of cardiac disorders, such as myocarditis, dilated cardiomyopathy, and dilated cardiomyopathy. Cardiomyocyte mortality, oxidative stress, inflammation, and mitochondrial dysfunction are all elements in the aetiology of HF that led to myocardial fibrosis and remodelling. HSPs can reduce heart dysfunction in HF and carry out a variety of additional functions, including regulating apoptosis and possessing anti-oxidant and anti-inflammatory properties. Not all HSPs are protective in HF, though; certain HSPs have detrimental effects on the development of HF. The pathophysiology of HF can be changed in two ways by even a small number of HSPs. The specific functions performed by HSPs in HF with different cellular and molecular microenvironments must thus still be clarified via further investigation. New therapeutic methods that focus on the regulation of HSPs would have a promising future in the prevention and treatment of HF [56].

HSP70 was positively correlated to the severity (progression) of HF ($r = 0.456$, $p < 0.001$). The area under the rate of change (ROC) curve was 0.601 ($p = 0.017$) in patients with stage B HF and 0.835 ($p < 0.001$) in those with stage C HF. HSP27 and HSP90 in the investigation did not show any appreciable alterations at any stage of HF. When considered collectively, plasma concentrations of HSP70 increased with the development of HF and may serve as a possible screening biomarker for HF early diagnosis [57].

The synthesis of HSPs in cardiomyocytes is increased when they are subjected to stressors. A tolerance for stress-induced cell damage is thought to result from such an increase in cellular HSP synthesis. Unknown is the precise function of cellular HSPs. Following coronary artery ligation (CAL), heart failure was developed in the current investigation, and HSPs in the healthy left ventricular myocardium were identified. The authors demonstrated that several modifications to myocardial HSP production take place as heart failure progresses. Only the increase in myocardial HSP60 production was linked to the onset of CHF [58].

Conclusion

The CgA, Catecholamines, Copeptin, Cortisol, L-FABP, SOD and catalase, Fibrinogen, MDA, and HSPs play a significant role in heart failure. However, this article did not report the glucose, HbA1c, triglycerides, cholesterol, prolactin, oxytocin, dehydroepiandrosterone sulfate, CRP, blood urea nitrogen and creatinine, acute phase proteins and more in HF pathogenesis.

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Conflict of interest

The authors state that they have no conflicts of interest.

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List of abbreviations

heart failure (HF), reactive oxygen species (ROS), chromogranin A (CgA)

liver-type fatty acid-binding protein (L-FABP), malondialdehyde (MDA), heat shock proteins (HSPs)

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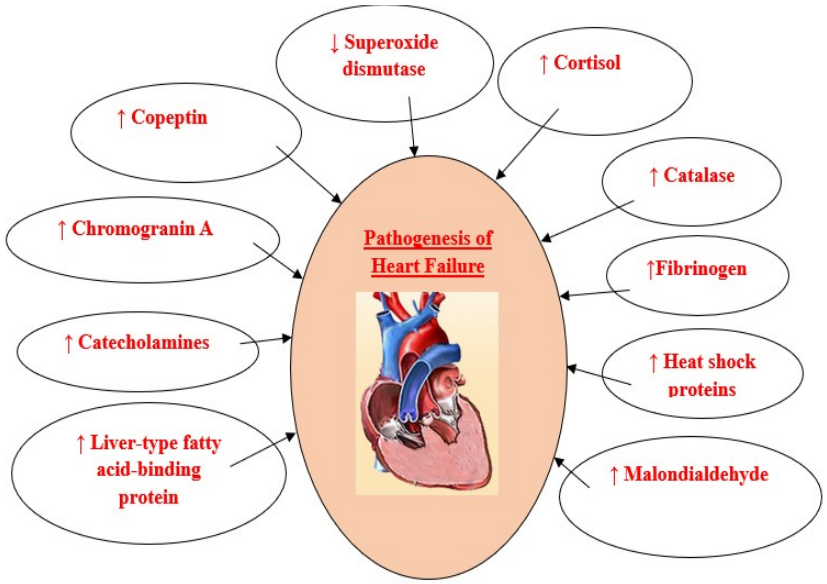

Figure 1. Serum/plasma levels of major biomarkers of stress in heart failure subjects– (source: designed by the authors with the help of articles)

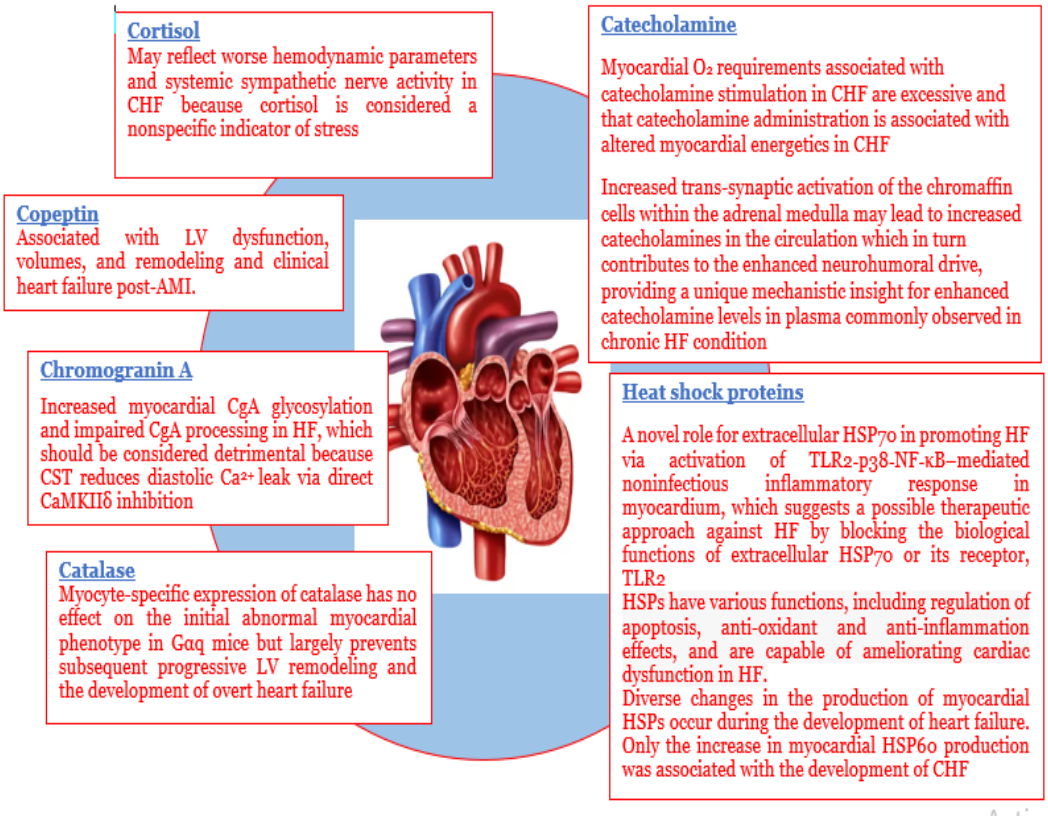

Figure 2. Overall summary of major biomarkers of stress role in the pathogenesis of heart failure (source: designed by the authors with the help of articles)