

Review Article

Biomarkers for heart failure

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ABSTRACT

The increasing rate of heart failure poses a lot of problems for health care system worldwide. Heart failure sign and symptoms depend upon the part which is being altered. Left side heart failure has different symptoms while right side failure shows different symptoms. Different classes of heart failure have been categorized depending upon different factors the most important one is functional classification. This classification is not reproducible hence four stages of heart failure has been defined. Before its worsening, heart failure can be predicted by using some natural substances in body due to altered conditions that act as marker of the disease. These substances are called biomarkers. These biomarkers may be divided into different seven categories including inflammatory products, elevated reactive oxygen species, heart remodeling products, and excessive collagen synthesis stimulants, myocardial cell injury products, neurohormones and cardiac stress biomarkers.

1. INTRODUCTION

The increasing rate of heart failure poses a lot of problems for health care system worldwide. Many people are suffering from this disease. There a lot of causes leading to this disease. Heart failure has many types and stages depending upon causes. A way to avoid this disease is the early prediction to the persons which may be at risk of heart failure. Biomarkers are very useful substances, present within the body, for early diagnosis of heart failure risk however they may exert negative effects themselves. This disease may lead to the death or hospitalization of great number of the patients suffering from it [1].

2. HEART FAILURE

It is also called as congestive heart failure (CHF) and is described as loss of ability of heart to pump blood sufficient to meet the body needs. In some cases, blood is not properly filled in heart and as a result heart has lower capacity to supply sufficient amount of blood with enough force. Both problems may occur at a time. Failure of heart does not refer that the heart cannot work. Heart is a contracting muscular organ present in all animals with a circulatory system and pump blood throughout the body by rhythmic contractions. Any factor interrupting its

normal pumping may leads to heart failure. Cardiac failure is common term stating the physical stage in which there is low heart output and fluid gets accumulated within the body [2]. It is usually caused due to increased oxygen and food requirements as compared to supply.

2.1 Causes of heart failure

There may be a number of causes leading to heart failure. Some common causes include heart diseases related to ischemia, cardiomyopathy and infarction of heart muscles, increased blood tension, and valvular problems of heart. Other causes include tobacco addiction increased body fats elevated body sugar level or arteriovenous malformation, valvular heart disease, viral myocarditis, amyloidosis, HIV cardiomyopathy, connective tissue disease. Abuse of drugs like alcohol etc, chemotherapeutic agents and arrhythmias include rare causes of heart failure [3]. Genetic, neurohormonal, inflammatory and biochemical changes may also be responsible for heart failure.

2.2 Signs and symptoms

Signs depend upon side of heart failure. Left sided heart failure may lead to respiratory signs including tachypnea, respiratory

distress, rales, pulmonary edema, cyanosis, cardiac asthma or wheezing. Additional signs are apex beat, gallop rhythm, heart murmurs etc. Right sided leads to peripheral edema, ascites, hepatomegaly, nocturia, jaundice, coagulopathy, increased jugular venous pressure. Left sided heart failure may lead to right sided heart failure hence patients commonly show signs and symptoms of both sided failure.

2.3 Classification of heart failure

Heart failure is classified by using different methods. The classification may depend upon the side of heart involved i.e. left heart failure versus right heart failure, or abnormality in contraction and/or relaxation i.e. systolic abnormality vs. diastolic abnormality. Classification may also be carried out due to problem in after load and preload called backward vs. forward heart failure. Extent of functional impairment may also lead to categorizing the heart failure [4]. Similarly, the extent of coexisting illness is also used for classification. Heart failure is categorized functionally as class I class II class III and class IV which are described in table 1.

Table 1. Classification of heart failure

Class	Characteristics
Class I	Daily routine activities don't show any symptom. There is no restriction on normal working routine.
Class II	A person suffering from class II heart failure is comfortable at rest or with little working load. There is a slight restriction on activity.
Class III	The person suffering from this feel comfort only at resting position.
Class IV	Symptoms occur at rest and any activity cause discomfort to the patient.

Although this classification is not much reproducible, its use is widespread. It does not reliably predict the proper walking distance or tolerance of exercise [5].

2.4 Stages of heart failure

There are four stages of heart failure [6].

Stage A: There is no structural and functional abnormality but the person has great risk for development of heart failure. It is called as pre-heart failure stage.

Stage B: Although there is no symptom but the patient may have a structural disorder.

Stage C: The patient suffers from structural heart problem and symptoms are present but can be managed by medical treatment.

Stage D: Patient has to be hospitalized or he must undergo heart transplant or palliative care.

The heart failure may be chronic or acute decompensate.

3. BIOMARKERS

Biomarker or biological marker is a term which refers to a variety of substances. In general biomarkers are molecular, cellular or biochemical changes occurring in human cells, tissues and body

fluids [7]. The biomarkers are actually indicators of normal body processes, altered body functions or pharmacological interventions. These can be measured and evaluated. Biomarkers include tools and techniques that help in the prediction, finding causes, diagnosing the disease, its development, deterioration and the results of therapeutic interventions.

4. CARDIAC BIOMARKERS

The biomarkers which are used to evaluate the heart function are called cardiac biomarkers. The earlier biomarkers which were discovered in many heart conditions were enzymes hence also called as cardiac enzymes but all of them are not enzymes e.g. troponin is not an enzyme.

4.1 Characteristics of cardiac biomarkers

Biomarkers should fulfill three requirements [8] to be clinically useful. First one is that the clinician must be provided with repeated and accurate measurements at affordable price and smaller time circle. Second the information, which is not present from a careful evaluation before, must be provided by it. The last one is that a biomarker must be helpful in making medical decision.

There are very few cardiac biomarkers which satisfy the above criteria, but many of them provide information about the patients which are at risk of heart failure, about its pathogenesis, heart failure diagnosis or monitoring therapy. Many biomarkers are themselves causative for the disease hence may be the therapeutic targets. Although there is no specific acceptable biomarker but they may be divided into seven classes. However, the seventh class is not fully defined. See table 2 for summary of cardiac biomarkers.

Table 2. Summary of cardiac biomarkers

No.	Category	Biomarkers
1.	Inflammatory biomarkers	C-reactive proteins, cytokines interleukin and tumor necrosis factor (TNF- α)
2.	Reactive oxygen species	Free radicals such as super oxide and non- radicals such as hydrogen peroxide, indirect markers are plasma-oxidized low-density lipoproteins, isoprostane level in plasma and urine, myeloperoxidase, isoprotane, xanthine and hypoxanthine
3.	Biomarkers of extracellular matrix remodeling	Peptide collagen type I
4.	Heart cell injury	Cardiac troponins T and I
5.	Neurohormones in heart failure	Norepinephrine plasma rennin activity, aldosterone, brain natriuretic peptides and arginine vasopressin
6.	Cardiac stress	Natriuretic peptides, Adrenomedullin and ST2
7.	Biomarkers under investigation	Chromogranin A, galectin-3, osteoprotegenin, growth differentiation factor 15 and adiponectin

5. TYPES OF CARDIAC BIOMARKERS

5.1 Inflammatory biomarkers

Inflammation is complex biological reaction of vascularized living tissue to local injury. Inflammation plays a key role in the pathogenesis and development of many types of cardiac failure. In 1956 a report was published in which it was described that c-reactive protein, a protein found in serum in different inflammatory responses, was detected in 30 of 40 patients suffering from chronic cardiac failure with high level of C-reactive protein heart failure was more severe. C-reactive protein was produced by the liver cells due to the proinflammatory cytokine interleukin and was described as an acute phase reactant. When a low cost, highly sensitive test is developed for CRP, its use as biomarker becomes more common. Different types of analytical test indicate that CRP is an independent analyst of side effects in patients suffering from acute or symptomatic chronic cardiac failure. In some patients who were at risk of developing heart failure, in addition to C-reactive proteins, cytokines interleukin and tumor necrosis factor (TNF- α) was also identified [9].

C-reactive proteins are harmful in context of exerting direct negative effects on endothelium of blood vessels. It reduces release of nitric oxide and causes an increase in endothelin-I production. It also induces endothelial adhesion molecules expression. This shows that C-reactive proteins may also be the therapeutic target as they play an important role in vascular disease. However high levels of C-reactive proteins not necessarily refer the risk of heart failure as these may be elevated due to some other reasons.

In 1990, elevated levels of systemic TNF- α were described to be associated with heart failure. Proinflammatory cytokines cause apoptosis and necrosis of heart cells; interleukin-6 appears to cause hypertrophy in myocytes [10]. TNF- α is responsible for left ventricular dilation due to matrix metalloproteinases activation. The levels of TNF- α and interleukin-6 can be used to predict asymptomatic patients at risk of cardiac failure. There are many approaches tested so far give disappointing result due either to neutral findings or even a worsening of heart failure. These results raised a number of questions related to the role of inflammatory in pathogenesis of heart failure and anti-inflammatory therapy is likely to be beneficial. FAS also called as APO-1 is a Tumor necrosis factor- α receptor family member found on different types of cells including cardiac cells. It is also causing apoptosis and leads to development of heart failure. Persons suffering from heart failure are found to have elevated FAS serum level and high levels are found in severe cases [11]. Reduction in FAS level is helpful in treatment or prevention of heart failure. Thus, level determination of C-reactive protein, inflammatory cytokines, FAS and their soluble receptors is useful to predict risk factors, development of disease and help in selection of appropriate therapy.

5.2 Reactive oxygen species

Oxidative stress refers to disturbed balance between the reactive oxygen species (ROS- including free radicals such as super oxide

and non- radicals such as hydrogen peroxide) and endogenous antioxidant defense mechanisms. Endothelial function is greatly affected by this imbalance. This altered balance also exerts injurious effect on the development of heart failure [12]. Oxidative stress leads to reduction of nitric oxide synthase activity which in turn leads to nitric oxide inactivation. Cellular proteins may also be damaged due to oxidative stress and lead to myocyte apoptosis and necrosis.

Some factors that cause oxidative stress include inflammatory and immune activation, and peroxynitric formation due to super oxide anion and nitric oxide interaction. Reactive oxygen species are difficult to be measured in humans, hence indirect markers are used. The oxidative stress indirect markers are plasma-oxidized low-density lipoproteins, isoprostane level in plasma and urine. According to the recent studies in organ system, ROS exert effects depending upon the concentrations, site of production and overall redox status of the cell. Levels of plasma myeloperoxidase and isoprostane release from body determine the heart failure severity. A pathological role is played by Xanthine oxidase which catalyses the formation of two oxidants i.e. xanthine and hypoxanthine [13]. High level of uric acid production causes an increase in xanthine oxidase activity and also causes altered hemodynamics. However, uric acid may be used as simple useful clinical excess oxidative stress indicator.

5.3 Biomarkers of extracellular matrix remodeling

Myocyte size and shape is determined by the extracellular matrix that forms a skeleton for myocyte as well. In a healthy person the matrix metalloproteinases and inhibitors of metalloproteinases are in a balance. Ventricular dilatation and remodeling may lead to an increased level of matrix metalloproteinases, playing a key role in development of cardiac failure. Matrix remodeling biomarkers include propeptide procollagen type I and plasma procollagen type III. At least 15 matrix metalloproteinases and several types of procollagen and inhibitors of metalloproteinases are found to be associated with ventricular remodeling. The peptide collagen type I act as serum biomarker for collagen synthesis. There is a positive correlation between peptide procollagen type I serum level and fibrous tissue fractional volume. The increased level of extracellular matrix breakdown as well as of excessive collagen synthesis is related to adverse effects of impaired ventricular function in patients suffering from heart failure. These markers are used as important target or therapy.

5.4 Heart cell injury

Heart cells or the cardiac cells are called myocyte that may get injured due to severe ischemia as well as inflammation, oxidative stress and neurohormonal activation. Specific and sensitive biomarkers of myocyte injury are the cardiac troponins T and I. They are greatly used in diagnosis, risk prediction and care of the patients suffering from acute coronary syndromes. Elevated troponin levels are also found in the patients with heart failure

without ischemia. Troponins are composed of three proteins: troponin C, I and T. Troponins are actually regulatory proteins of muscle contraction which are tightly bound to contractile apparatus. It is also found in cytosol in very small quantity. The troponin C is same for both cardiac and skeletal muscle but troponin T and I counterparts are different structurally and antigenically. For cardiac troponin assay skeletal muscle troponin must not be present. Cardiac troponin is found in blood due to pathological breakdown of skeletal muscles [14].

5.5 Neurohormones in heart failure

In 1960s, it was found that plasma NEP level increased in the patients suffering from heart failure. Excretion of norepinephrine in urine was also found to be elevated [15]. Other neurohormones involve plasma rennin activity, aldosterone and brain natriuretic peptides (BNP).

Heart failure is intensified by Arginine vasopressin. It has antidiuretic and vasoconstrictor property. Acute symptoms are relieved by blocking vasopressin 2 receptor but natural history of serious cardiac failure remains the same. Neurohormones are unstable in plasma and are difficult to measure on routine bases. They can be used as therapy target and biomarkers of heart failure.

5.6 Cardiac stress

Biomarkers of myocyte stress include natriuretic peptides, adrenomedullin and ST2.

5.6.1 Natriuretic peptides

Ventricular dilatation, hypertrophy or increased wall tension causes the prohormone to be released. A circulating endoprotease called corin cleave prohormone BNP. Increasing age is also a cause of increasing level of circulating BNP commonly in patients with myocardial fibrosis or renal dysfunction. While interpreting the natriuretic peptides, all the physiological conditions and disease states must be considered. Current guidelines recommended these biomarkers of heart failure testing as assays for these are available commercially [16]. BNP measurement is useful in the diagnosis and risk prediction and is better predictor of death than in plasma norepinephrine or endothelin-1.

5.6.2 Adrenomedullin

Proadrenomedullin is a precursor of adrenomedullin, a peptide of 52 amino acids, produced and found in lungs, heart, adrenal medulla, and kidney synthesized due to cardiac pressure and volume overload. It has ionotropic and natriuretic properties and is a potent vasodilator. 45 to 92 amino acids fragment of proadrenomedullin located at midregion is easy to measure and is more resistant against destruction. In combination with NT-pro-BNP, midregional proadrenomedullin provides analytical value.

5.6.3 ST2

When monocultured monocytes are subjected to mechanical strain, a protein is secreted that is ST2 which is member of interleukin receptor family. This receptor has a ligand which is interleukin-33; starved heart muscles stimulate and produce it. When soluble ST2 is infused they decrease inflammatory cytokines, interleukin-6 and interleukin-12 which in turn reduce inflammatory responses. The ST2 biomarker is an important predictor of heart failure and need for cardiac transplantation.

5.7 Biomarkers under investigation

Other than above biomarkers, some others are being studied. These include chromogranin A; found at higher levels in patients suffering from heart failure, it is hormone produced by myocardium having negative inotropic effect [17]. Others are galectin-3, osteoprotegerin (a member of TNF receptor super family), adiponectin, and growth differentiation factor 15. These biomarkers need further study.

6. CONCLUSION

Heart is most vital organ of the body. Any factor effecting its normal functioning may lead to the heart failure. Heart failure is one of the growing and challenging problems for the public health care. There are some substances which can help us to predict whether a person is at risk to develop heart failure. There are many biomarkers which predict heart failure by measuring its level in plasma. These include inflammatory cytokines, high plasma level of reactive oxygen species, heart remodeling products and biomarkers of collagen biosynthesis, which can be used as predictor of heart failure but still require further studies.

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