

REVIEW ARTICLE**Heart Failure: A Review on Pathogenesis and Treatments****Praveen Kumar^{*1}, Ankur Rohilla¹, Seema Rohilla², Ashok Kushnoor¹**¹Department of Pharmaceutical Sciences, Shri Gopi Chand Group of Institutions, Baghpat-250609, UP, India²Department of Pharmaceutical Sciences, Hindu College of Pharmacy, Sonapat-131001, Haryana, India

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ABSTRACT

Heart failure (HF) has been considered as a life threatening disease that may occur due to improper blood supply to the body from the heart in order to maintain the normal physiological function or may be due to increase demand of oxygen and nutrient in the body. However, HF can be classified mainly as acute and chronic heart failure, but certain other classifications including side of the heart involved, on the basis of insufficient contraction, pressure overload and cardiac output has also been documented. Numbers of causative factors that lead to HF include ischemic heart disease, cigarette smoking, hypertension, obesity, diabetes and valvular heart disease. Further, various signaling mechanism are involved in the pathogenesis of HF including insulin growth like factor I (IGF-I), renin-angiotensin system (RAS), mitogen activated protein kinase (MAPK), C-jun-N-terminal kinase (JNK), fibroblast growth factor (FBF) and tumor necrotic factor-alpha (TNF- α). Moreover, numerous treatment strategies for HF involve angiotensin converting enzyme (ACE) inhibitors, beta (β) blockers and aldosterone receptor antagonist (ARA). The present review on HF illustrates various signaling mechanisms leading to HF alongwith treatment strategies.

Key words: Heart failure, Signaling mechanisms, Treatment.**INTRODUCTION**

Heart failure (HF) is a pathological condition that has been known to exist from ancient times [1,2,3]. HF has been regarded as a condition in which heart is unable to produce sufficient amount of blood to fulfill the adequate demands of body [4-5]. The HF has been well reported to occur due to various pathological complications such as myocardial infarction, ischemic heart disease, valvular heart disease and cardiomyopathy [6-7]. Additionally, other causes involve viral myocarditis, protein build up in coronary arteries, connective tissue disease, chronic alcoholism and arrhythmias. Certain pathological conditions are also responsible for the development of HF like that of cardiac hypertrophy, in which the ventricle wall of the heart get thickened and the heart gets unable to pump the blood properly, leading to blood insufficiency to the tissue ultimately causing the development of HF [1,2]. HF can be recognized from a number of symptoms includes swelling of legs and shortness of breath get. Moreover, the appearance of the symptoms of the HF can be further categorized on the basis of conditions due to which it is arising, like, the side

of heart involved, i.e., left ventricular failure, right ventricular failure or biventricular failure [8-9]; acute and chronic HF [10-11]; insufficient contraction and relaxation, i.e., systolic dysfunction or diastolic dysfunction; and on the basis of pressure overload, i.e., preload and after load [12,13]. Various signaling mechanisms have been found to be involved in the pathogenesis of HF that include beta-adrenergic-receptor kinase (β -ARK), IGF-1, RAS, MAPK, JNK, FBF and TNF- α [2]. Various treatment strategies for the HF have been demonstrated include diuretics, including loop diuretics, thiazide diuretics, potassium (K^+) sparing diuretics [14], aldosterone antagonists [15], vasodilators; calcium channel blockers (CCBs); β -blockers [16]; ACE inhibitors [17]; angiotensin (Ang)-II receptor blockers [18], and cardiac glycosides [19]. Moreover, the surgical treatment of HF includes coronary artery bypass surgery (CABS) [20]; surgery of the ventricles; left ventricle (LV) reconstruction surgery [21], implantable left ventricular assist devices [22], and heart transplant [23]. The review crucially aims to highlight the pathology of HF. Moreover,

signaling mechanisms and treatment strategies have also been discussed in the review.

CLASSIFICATION OF HF

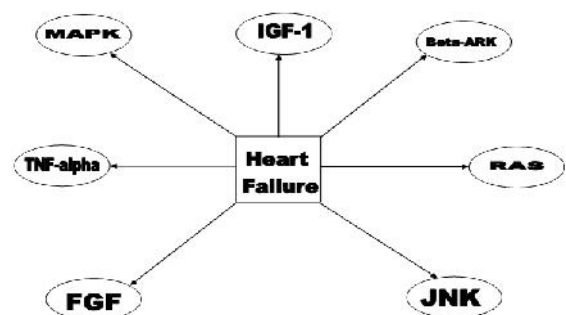
HF can be classified on various basis; the very first being the worldwide accepted classification introduced by the New York Heart Association (NYHA), which is mainly based on the appearance of symptoms. According to NYHA, HF can be classified into four classes^[24], that are; Class I, in which no limitation is experienced in any of the regular activity^[25,26]; Class II, in which there is slight limitation in the activity and patient feel mild discomfort during regular activity and feel relief during rest^[27,28]; Class III, in which there is subsequent limitation to do the regular activity and patient feel relief from the symptoms during rest^[29]; and Class IV, in which a mild activity of the patient results in the discomfort and symptoms occur even rest^[12]. Further, HF can be classified according to the American Heart Association (AHA), according to whom, four stages of HF involve; Stage 1, in which patient is at high risk of developing HF, but there will be no heart related disorder^[30,31]; Stage 2, in which the patient suffers from the heart disorder but there will be no appearance of the symptoms^[32]; Stage 3, in which the patient bears the symptoms of HF due to some heart related disease, which can be treated by medicinal management; and Stage 4, which can not be treated with drug treatment and patient requires heart transplantation and hospitalization^[13]. In addition, HF can be further categorized on the basis of conditions due to which it arises, like, the side of heart involved, acute and chronic HF, insufficient contraction and relaxation and on the basis of pressure overload^[8-13].

SIGNALING MECHANISMS INVOLVED IN HF

Various signaling mechanism has been found to be involved in the pathogenesis of HF that include β -ARK, IGF-1, RAS, MAPK, JNK, FGF and TNF- α (Fig 1)^[2]. It has been suggested that β -ARK acts as one of the signaling component of HF. B-ARK has been shown to interact with the phosphoinositide-3-kinase (PI3-K) and forms a complex. The selective inhibition of the β -ARK in assess of PI3K explores the cardiac function towards normal evidencing the role of β -ARK in the pathogenesis of HF^[33]. IGF-1 is mainly involved in the improvement of cardiac growth and enhancement of myocardial contractility by increasing the intracellular Ca^{2+} and resulting in contractile proteins that stimulate cardiac growth. This contention supports the fact that IGF-I plays a key role in order to maintain the normal

functioning of failing heart^[34]. Moreover, it has been shown that renin-angiotensin system (RAS) is involved in the pathogenesis of HF. The blockage of RAS with Ang II receptor antagonist has been demonstrated which confirmed the modulatory role of RAS in the pathogenesis of HF^[35]. Further, MAPK has been reported to be involved in the HF by regulating various cellular functions that include proliferation of cell and its differentiation. In addition, MAPK has been involved in cardiac hypertrophic responses and in the cardiac remodeling confirming the role of MAPK in HF^[36]. However, the modulatory role of JNK in HF is still unidentified, but it has been found that MAPK 7(D) is mainly responsible to activate the JNK which further leads to cardiac dysfunction. Furthermore, it has been demonstrated that activation of JNK may results in the loss of connexin 43 proteins and gap junction without having any effect on the expression of the gene protein. Thus, it can be concluded that JNK plays a key role in the cardiac remodeling and acts an important mediator in the pathogenesis of HF^[37]. Moreover, FGF has been shown to act as a mediator in cardiac remodeling. In support, it has been found that FGF plays an important role in various pathological conditions associated with heart like hypertrophy and ischemia-reperfusion injury. In addition, it has been suggested that elevation in blood FGF level is directly connected to the development and progression of cardiac disease^[38]. Furthermore, TNF- α has been considered as one of the key signaling mechanisms involved in the pathogenesis of HF and other cardiac diseases. The release and downstream of TNF- α has been noted to activate its two receptor subtype that may improve vascular cell functioning and endothelial blood cells, which are the characteristics features of the early stages of heart failure, which may further be characterized with the formation of atherosclerotic plaque ultimately leading to the development and progression of HF^[39].

Fig 1: Signaling mechanisms involved in the pathogenesis of Heart Failure



TREATMENT OF HF

Two approaches for the treatment of HF have been vitally studied which include medical and surgical strategies. Medical treatment strategy for HF include various classes of drugs like; diuretics, including loop diuretics, thiazide diuretics, potassium (K⁺) sparing diuretics; aldosterone antagonists; vasodilators; calcium channel blockers (CCBs); β -blockers; ACE inhibitors; angiotensin (Ang)-II receptor blockers; and cardiac glycosides^[14-19]. Furthermore the patient is suggested to do certain modification in his life such as to avoid heavy exercise and other certain activities that may lead to the development and occurrence of HF. Another approach for the treatment of HF involves the surgical treatment that includes CABG, LV reconstruction surgery, implantable left ventricular assist devices and heart transplantation^[20-23]. In CABG, the revascularization of the coronary arteries is performed in order to maintain the normal cardiac functioning^[20]. Moreover, the estimated amount of the physiological myocardium and the study can be done by single photon computed tomography study (SPECT) and positron emission tomography^[40]. The left ventricular surgery involves achieving the preshape of the ventricle, which is used when the patient is preliminarily suspected to the heart disease like myocardial infarction^[41-42]. Furthermore, the absolute treatment for HF includes heart transplantation in which the whole human heart is transplanted from the normal heart.

CONCLUSION

Heart Failure is one of the most well known diseases related to heart occurring worldwide today. In the present review we have discussed some signaling mechanisms that are responsible for the progression and alteration of the HF. However, for the future point of the view, these signaling mechanisms may play a key role in the therapeutic treatment of the HF, but selective drugs with low toxicity level may support the prevention and treatment form such a life threatening disease. Moreover, the potential use of the drug therapy and basic knowledge of the signaling mechanisms of HF would prove helpful in order to improve the life period of a patient presented with HF.

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