IJPSR (2022), Volume 13, Issue 8 (Review Article)

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 08 November 2021; received in revised form, 01 January 2022; accepted, 27 January 2022; published 01 August 2022

CARDIAC REMODELING: A HARMFUL OR PROTECTIVE MECHANISM OF MYOCARDIUM

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Keywords:

Cardiac remodeling, Hypertrophy, Pathophysiological, Myocytes

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ABSTRACT: Cardiac remodeling is a progressive morphological change of the myocardium in response to various pathophysiological overloads. Cardiac remodeling occurs due to various mechanisms associated with GPCR and growth receptors. Fundamentally cardiac remodeling is an adaptive mechanism of the myocardium against various overloads. However, depending upon the frequency, strength, and type of overload, these mechanisms can be physiological or pathological. Physiological cardiac remodeling results from controlled overloads that aggravate myocyte hypertrophy and angiogenesis. Pathological remodeling occurs because of excessive overload-induced mechanisms responsible for the over-activation of the immune system and cardiac fibrosis. This review covers the harmful and protective effects of cardiac remodeling and several anti-hypertrophic mechanisms co-occurring. Reviewed literature designates cardiac remodeling as a protective mechanism of myocardium against cardiac overload. However, the overactivation of several inflammatory and other related mediators during cardiac remodeling is liable for its harmful aspects.

INTRODUCTION: Remodeling is modifications in structure due to rear-arrangement of the normally existing state. Myocardial remodeling is modifications in the structure of the myocardium because of pathological or physiological overload on Cardiomyocytes. Cardiac remodeling is usually recognized as an element of the clinical advancement of heart failure (HF) [1]. Cardiac remodeling is mainly prejudiced by hemodynamic load and neurohormones activation, which further leads to activation of various mediators of remodeling.

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DOI: 10.13040/IJPSR.0975-8232.13(8).2988-99

This article can be accessed online on www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.13(8).2988-99

Cardiac myocytes are the key mediators involved in the remodeling process. Further depending upon the type of overload, various other Components, including interstitium, fibroblasts, collagen, coronary vasculature and relevant processes including ischemia, cell necrosis, and apoptosis, are also involved in the pathophysiology of cardiac remodeling.

Cardiac remodeling is optionally associated with myocardial infarction (MI), Pressure overload (aortic stenosis, hypertension), inflammatory heart muscle disease (myocarditis), idiopathic dilated cardiomyopathy, or volume overload (valvar regurgitation). Although etiologically, these diseases are different and may share various molecular/biochemical pathways and several mechanical events [2-4]. Physiologic remodeling is the outcome of compensatory changes in the magnitudes and function of the heart, as seen in

athletes. Besides it, several pathological studies show that left ventricular (LV) remodeling initiates rapidly within a few hours of infract and continues to progress. The initial remodeling phase leading to reparation of the necrotic area and scar formation is considered beneficial. This cellular rearrangement of the ventricular wall is concomitant with continued or improved cardiac output but with significantly increased LV volumes. Further sustained large infarcts aggravate greater dilation and increase systolic and diastolic stress as compared to small infarcts. Post infarction dilation leads to a progressive increase in the end-systolic volume index and decline in ejection fraction, which are predictors of mortality [5, 6]. On remodeling, the heart changes its geometry from elliptical to more spherical, ultimately altering the Ventricular mass, composition, and volume, which may adversely affect cardiac function. Remodeling covers cellular changes comprising myocyte hypertrophy, necrosis, apoptosis, fibrosis, increased fibrillary collagen, and fibroblast proliferation. Increased angiotensin II was also reported to alter gene expression via activation of second messenger systems, which further elevate the symptoms of cardiac remodeling. Further various associated pathophysiological changes depending on their stimulus may protect or harm the Cardiomyocytes [3, 5, 7, 8].

Associated Pathophysiological Changes in Cardiac Remodeling:

1. Hemodynamic Load: As a result of hemodynamic load, left ventricular dilation in patients with anterior wall myocardial infarction may continue progressively and lead to compensatory (reactive) ventricular hypertrophy. The importance of remodeling as a pathogenic mechanism is unclear, and the factors leading to may be the foremost determinants of Heart Failure prognosis rather than ventricular dilation itself. Prolonged Cardiac dilation without hypertrophy further stimulates various mechanisms leading to increased myocardial wall stress. Without therapies for reducing ventricular dilation, decreasing wall stress, and promotion of favorable neurohormonal pattern, this process progresses towards overt chronic Heart Failure [9, 10].

2. Neurohormonal Activation: Pathophysiological activation of Neurohormones has been reported to modulate cardiac output and is a major component of the progression of cardiac remodeling. Plasma norepinephrine levels, responsible for increasing adrenergic activation are raised in heart failure and left ventricular dysfunction patients. These elevated levels of norepinephrine lead to a poorer long-term prognosis. Recently, Neurohormonal activation was also reported to decrease the progression of post-MI in patients with a good prognosis. Further, angiotensin II was shown to increase DNA and protein synthesis in myocardial fibroblasts and myocytes, indicating its importance for cellular responses with its local production resulting in proliferation and growth of Cardiomyocytes. Angiotensin II also increases coronary artery permeability, allowing diffusion of growth factors into the myocardial interstitium. Besides these beneficial effects, angiotensin II was also reported to cause necrosis and fibrosis of cardiac myocytes through the various cytotoxic mechanism. Angiotensin II was also shown to increase aldosterone production, which further stimulates collagen synthesis by myocardial fibroblasts and causes electrolyte balance leading to severe hemodynamic consequences and ultimately death of myocyte [11, 12].

3. Additional Changes: Endothelin, cytokines (TNF: tumor necrosis factors and interleukins) and nitric oxide (NO), and various other factors involved in oxidative stress are associated with the Renin-angiotensin system (RAS) and the sympathetic nervous system (SNS) and are currently under investigation for their pathophysiological potential in cardiac remodeling. Endothelin, known potent vasoconstrictor peptides, are found to be elevated inpatient of Heart Failure, and antagonism of Endothelin is beneficial in modulating cardiac remodeling.

Cytokines are proteins secreted by cells in response to several stimuli's including environmental stress, to counter the conditions. Further Circulating levels of the cytokines, specifically TNF-alpha, are found to be raised in cardiac remodeling [13]. Data have also shown that pathophysiologic stimulation of TNF-alpha provokes concentrations and time-dependent increases in left ventricular remodeling in animal models of HF. Another associated factor termed Oxidative stress (imbalance between free radicals and antioxidants) is the increasingly

emerging condition for the modulation of left ventricular functioning and progression of cardiac remodeling. Cardiomyocyte sustainability depends on a complex interaction of inducers and suppressors of apoptosis, which are further, controlled byvarious cytokines, including TNF-alpha [14]. Cytokines upsurge apoptosis and have necrosis by their death mechanisms within the cytoplasmic portion of the TNF receptor-1. Overall, these processes modulate cardiomyocytes' composition and functioning, which may be beneficial if activated in physiological conditions or harmful if activated pathologically at very high concentrations and are associated key role players in the pathophysiology of cardiac remodeling [15].

Component of Cardiac Remodeling:

Cardiac Myocytes: Various heart cells, including Myocytes, are a main key role player in the pathophysiology of cardiac remodeling. Myocytes are responsible for cardiac contractility and heart mass. In response to various load stimuli, myocytes become elongated or hypertrophied to maintain stroke volume (Physiological cardiac remodeling), a compensatory process. But consistent cardiac load lead to decreased myocyte number and hence cause loss of contractility (Pathological remodeling). Surviving myocytes may undergo pathological hypertrophy and lead to the thickness of the ventricular wall and ultimately cardiac remodeling [16, 17]. Based on the synthesis of new contractile proteins and the assembly of new sarcomeres cardiac myocytes, adapt some specific patterns, whether these are the elongated or increased diameter. Sustained cardiac wall stress without sufficient protective mechanisms can lead to energy imbalance and ischemia in myocytes, ultimately deteriorating cardiac remodeling [18, 19].

Fibroblast Proliferation and Collagen Degradation: Both fibroblasts and endothelial cells are activated in reply to an ischemic insult. Fibroblast stimulation has been reported to increase collagen synthesis, which further leads to fibrosis of both infarcted and non-infarcted regions of the ventricle and ultimately worsens the mechanism of cardiac remodeling [20, 21]. Myocytes are supported by a network of connective tissue composed of large fibrillary collagen, which is synthesized and degraded by interstitial fibroblasts. Myocardial collagenase is an important proenzyme activated in response to myocardial injury that contributes to enlarged chamber dimension in distending pressure and is thought to be a possible cause of myocyte slippage and worsening of cardiac remodeling hence leading to chamber remodeling [22].

Aspects and Associated Signaling of Cardiac Remodeling: The heart is an energetic organ accomplished of adapting pathophysiological stress and is capable of remodeling its shape and size in response to these stimuli to preserve its function. The stimulus may be extrinsic signals in the form of neuroendocrine agonists and growth factors that act through membrane-bound receptors on cardiac myocytes or intrinsic stress associated with mechanical stretch. Further, these signals are transmitted by Intracellular transduction cascades throughout the cytoplasm and nucleus, which alter cardiac gene expression, metabolism, protein turnover and finally cause remodeling of the heart [23]. Cardiac remodeling is a protective mechanism by the heart in response to pathophysiological stimuli that may be converted to harmful in case of prolonged, sustained, or very resilient stimuli and can worsen cardiac remodeling and cause heart failure [24].

Protective Aspect and Associated Signaling of Cardiac Remodeling: The pathophysiological load has been led to increased chamber volume with increased or no alteration in wall thickness. Hypertrophy imposed by various pathologic stimuli is somewhere altered from physiologic hypertrophy. The aspect of stimuli inducing “physiological” and “pathological” hypertrophy depends on the nature and chronicity of the stress [12, 25]. For example, chronic exercise may cause excessive stress on myocytes and can convert physiologic conditions to Pathological conditions of cardiac remodeling. The data found that it was the nature of the stimulus that decides the pathophysiology of cardiac remodeling. Physiological hypertrophy of myocytes is mainly mediated by insulin-like growth factor-1 (IGF-1) and growth hormones (GH), with associated signaling pathways of bi-phosphoinositide3-kinase (PI3K) / Akt. IGF-1 like growth factors and insulin bind to specific membrane-bound tyrosine kinase receptors and stimulate the lipid kinase PI3K subgroup.

Further, PI3K phosphorylates the membrane phospholipid phosphatidylinositol 4, 5 bisphosphate and attracts the protein kinase Akt (protein kinase B) and its activator, 3-phosphoinositide-dependent protein kinase-1 (PDK1), to the cell membrane and ultimately leading to phosphorylation and activation of Akt. The important role of the IGF-1/PI3K/Akt pathway has been reported in exercise-induced hypertrophy in constitutively active or dominant-negative mutants of PI3K in mice [10, 26]. Further cardiac-specific active PI3K was also reported to increase heart size, while dominant-negative PI3K resulted from smaller hearts. It was reported that the modulation of heart size is mainly associated with myocyte size and is not affected by interstitial fibrosis or contractile dysfunction. Further cardiac expression of dominant-negative PI3K was found to attenuate exercise-induced hypertrophy but didn't have such a role in pathological pressure overload-induced hypertrophy, which demonstrates the specificity and significance of this pathway for adaptive exercise-induced hypertrophy [27]. Besides it deletion of the IGF-1 receptor was also reported to inhibit exercise-induced cardiac hypertrophy. Overexpression of Cardiac-specific active Akt (Protein kinase b) mutants induced myocyte growth and is a protective mechanism of the myocardium, however at elevated or sustained levels, Akt expression induces pathological growth. It may be harmful to myocardium [28, 29]. Besides, the normal expression of Akt also conferred protection from ischemia-induced cell death. Therefore, the actions of Akt are complex and have a significant role in adaptive physiologic hypertrophy. Adaptive physiologic hypertrophy was a protective mechanism for the heart. It increases the size and volume of myocytes with proper angiogenesis by activation of VEGF (Vascular endothelial growth factor) and strengthens the heart [30]. The whole protective mechanism of the myocardium is summarized in **Fig. 1**. Based on enlargement, cardiac hypertrophy can be distinguished into two categories, as shown in **Fig. 2**.

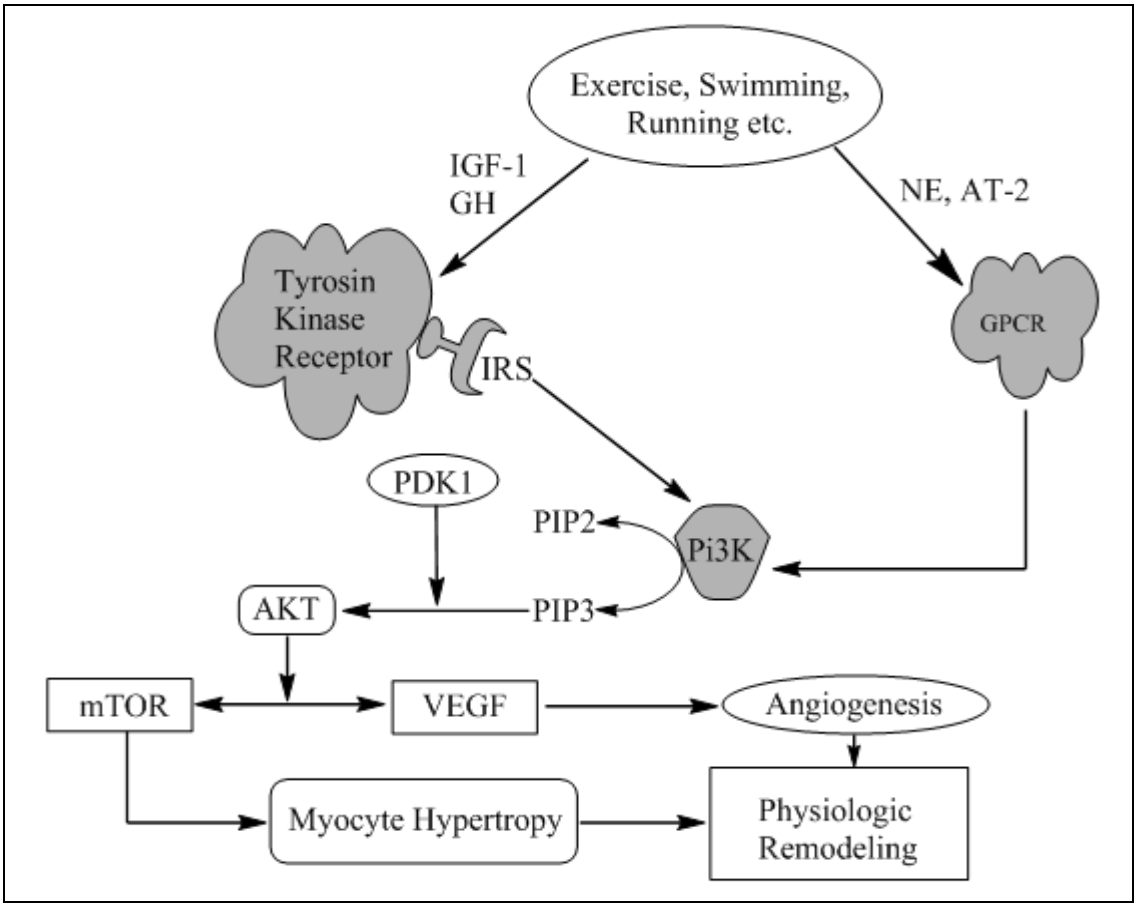

FIG. 1: PROTECTIVE ASPECTS OF CARDIAC REMODELING *IGF-1= Insulin like growth factor-1, GH= Growth Hormone, NE= Norepinephrine, AT-2= Angiotensin-2 Receptor, IRS= Insulin Receptor Substrate, GPCR= G-Protein Coupled Receptor, Pi3K= bi-phosphoinositide3-kinase, PIP= Phosphatidylinositol phosphate, PDK= Pyruvate dehydrogenase kinase, AKT= serine/threonine kinase, mTOR= Mammalian target of rapamycin, VEGF= Vascular Endothelial Growth factor.

a) Concentric Hypertrophy: Various static physical exercises, including weight lifting and bodybuilding, when performed chronically, are known as resistance training, which is a specialized method of condition designed to increase muscle strength and power. Resistance training results in hemodynamic modification and elevates blood pressure (BP), leading to a condition of pressure overload on the heart, which finally results in the parallel addition of sarcomeres [31].

This addition of sarcomeres further predominantly increases the cell width of cardiomyocytes and consequently increases the left ventricular wall thickness without reducing the size of the internal cavity in diastole [32]. The increased cardiomyocyte cross-sectional area by pressure overload increases the wall thickness and hence causes concentric hypertrophy. Hypertrophy in high-level strength athletes sometimes presents a macroscopic structure that looks similar to pathological hypertrophy and is sometimes incorrectly interpreted as pathological hypertrophy [33]. It was also reported that cardiovascular alterations in response to physiological stimulus depended on the type of training or exercise and are not influenced by stress, as circulating catecholamine and adrenal hormones remain unchanged. MHC (myosin heavy chain), a major contractile protein in the heart, has been reported as an essential protein for the efficiency of cardiac performance [34].

The MHC ratio varies in response to the extent of pathophysiological stimulus and is an important factor in the case of cardiac remodeling Studies have shown a decrease in MHC ratio under pathological conditions accompanied by higher expression of fetal gene reprogramming and hence impaired cardiac performance. Hence, resistance training induces physiological concentric cardiac hypertrophy and can be used as a noble model to study pathophysiological concentric hypertrophy and associated transducing signaling pathway [35]. Hypertrophy can be the result of several pathophysiological factors and associated pathways. However, pressure overload-like response is most consistent with concentric cardiac hypertrophy. Besides its extracellular signal-regulated kinases 1/2 (ERK1/2) signaling, a branch of the greater mitogen-activated protein kinases (MAPKs) has also been reported as a key mediator of cardiac remodeling [35]. The MAPK cascades are composed of multiple levels of kinases constituting a network of phosphorylation-based amplification. After receiving input from membrane-associated G-proteins receptors, MAP3K activates MAP2Ks, which activate the MAPKs. The MAPK cascades are generally sub-classified into three main branches, consisting of p38 kinases, c-Jun N-terminal kinases (JNKs), and ERK1/221 all of which ultimately has a key role in the modulation of cardiac remodeling.

Supplementary to this, some other kinases are also involved in this cascade, including ERK5 that MEK5 and ERK3/4 activate. ERK1/2 cascade is stimulated by activated small G protein Ras which further recruits the MAP3K Raf-1 to the plasma membrane where these final messengers are activated. Ultimately MAP3Ks phosphorylates and activates the dual-specificity kinases MEK1 and MEK2 (MAP2Ks) that further activates kinases for ERK1/2 phosphorylation and play a vital role in profound concentric hypertrophy. Various studies have also shown that pressure overload stress increases the width and surface area of Cardiomyocytes without any signs of pathological hypertrophy (fibrosis or sudden death), which suggests the beneficial effect of MEK1- ERK1/2 pathways in the compensated concentric hypertrophy response [36].

b) Eccentric Hypertrophy: Various dynamic or isotonic exercises *e.g.*, swimming, cycling, and running, increase heart rate and stroke volume, which are two important components of cardiac output. This leads to an increase in the effectiveness of cardiac muscle and a decrease in peripheral vascular resistance, which increases venous return to the heart and ultimately causes volume overload stress on the heart. Further, this volume overload stress leads to eccentric left ventricular hypertrophy [37]. Aerobic training-induced eccentric cardiac hypertrophy is predominantly characterized by a series of sarcomeres additions in the myocyte. This addition of sarcomeres increases myocyte length and increases the cardiac mass, resulting in increased chamber volume [32, 38]. Few studies have shown no such association between the pathway of eccentric hypertrophy and activation of fetal marker genes of pathological cardiac hypertrophy. MHC (Myosin

heavy chain), which is associated with increased myosin ATPase activity, enhancement of contractility and ventricular function, increased aerobic training and related exercises [39]. Chronically performed aerobic training induces cardiovascular changes; resting bradycardia has been considered to be the main effect of aerobic exercise training adaptation. Specifically, resting bradycardia induced after aerobic training is found to be due to reduction in sympathetic cardiac effects, increased cardiac vagal effects, reduction in intrinsic heart rate, and increased atrioventricular conduction time. Studies have shown that total heart volume is a key predictor of peak oxygen uptake and maximal work capacity of myocytes; hence Long-term aerobic training leads to balanced physiological enlargement of the heart [39, 40].

Most physical exercise is a combination of dynamic and static components; physiological hypertrophy mostly occurs in a combination of different degrees of both concentric and eccentric hypertrophy or can be called mixed cardiac hypertrophy, as observed in triathletes. The degree of physiologic hypertrophy observed depends on the intensity duration and the type of physical training program and is directly related to aerobic capacity [41]. Further swimming-based training has been shown to induce much robust cardiac hypertrophy compared to treadmill-based training. Studied literature suggests that eccentric hypertrophy is categorized by a preferential addition of a series of sarcomeric units, which ultimately elevates the shortening capacity of the myocyte and hence preserves ventricular function. However, sometimes elongation of myocytes that is eccentric hypertrophy was also found to be a marker of transitional decompensation and heart failure as a result of compensated hypertrophy in pressure overload conditions [42, 43].

Hence, it is important to differentiate between adaptive elongation *i.e.* eccentric hypertrophy and failure associated elongation. Besides it, various mediators of concentric hypertrophy, including ERK1/2 and related MEK5-ERK5 branch of the MAPK cascade, appear to induce eccentric hypertrophy preferentially. Overexpression of ERK5 was also found to cause ventricular dilation by 6 weeks of age in mice with enormously thin walls of both ventricular chambers. Other than abnormal hypertrophy of Cardiomyocytes, few studies had shown the healthy effect of activated MEK5 on Cardiomyocytes. While data indicates that the growth changes in Cardiomyocytes may be modulated by selected molecular pathways, leading to organ remodeling as in the case of eccentric/dilated type of growth [44-46].

Harmful Aspect and Associated Signaling of Cardiac Remodeling: Besides the protective mechanism of remodeling, depending on the type of stimulus, this protective mechanism may convert to the harmful mechanism of cardiac remodeling. Cardiac remodeling associated with pathological stimulus involves various abnormal cellular and molecular changes. These abnormal changes consist of myocyte growth without significant proliferation, re-expression of fetal genes, alterations in the expression of proteins involved in excitation-contraction (E-C) coupling, Improper angiogenesis, and changes in the metabolic energy state of the myocyte [47]. These changes in myocytes are escorted by changes in the extracellular matrix (ECM) and ultimately lead to myocyte death due to necrosis or apoptosis.

Macroscopically myocardium reacts in various ways in response to injury and stress. The injury area instantly after a myocardial infarction expands, leading to regional dilation and thinning of the infarcted zone. Upon subsequent scarifies and remodeling heart undergoes various geometrical changes and turns into less elliptical and more spherical with thinner walls. In the same way, in volume overload-induced hypertrophic remodeling, there is an increase in the ventricle's internal radius, which results in eccentric hypertrophy [48, 49]. Further, in pressure overload-induced hypertrophic remodeling, there is an increase in left ventricular wall thickness with a negligible increase in chamber size, and this process is called concentric hypertrophy. Primarily pathological stimuli result in reduced myocyte number, slipping between myocytes and ECM, and changes in wall architecture [50]. Upon consistent stimulus, concentric hypertrophy may convert to eccentric hypertrophy. It may lead to frank dilation with associated systolic heart failure, as observed in long-term pressure overload stress by aortic banding in animals **Fig. 2** [51]. The adaptive and maladaptive aspects of concentric hypertrophy are

still extremely controversial as one study also demonstrate that by increasing mass and normal systolic function of left ventricular for 5 years only 12.3% of patients show the highest quartile of left ventricular mass-developed or any detectable left ventricular dysfunction and only 6.9% of these patients developed clinical heart failure. The observed data of the study emphasize the need to differentiate the pathways associated with the initial compensated hypertrophic growth phase from decompensation, dilation, and extreme ventricular remodeling pathways [29, 52].

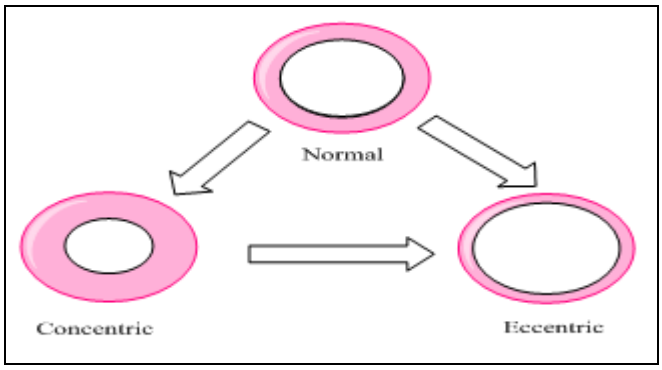

FIG. 2: MORPHOLOGICAL TYPES OF CARDIAC REMODELING

Various pathways are proposed for altering the pathophysiology of cardiac remodeling; one pathway is associated with Calcineurin and CaMKII, which was thought to modulate the growth of the myocyte without any other signs of pathology. Further, in the calcium / calmodulin-activated protein phosphatase calcineurin (PP2B) pathway, Calcineurin is triggered by continuous elevations in intracellular calcium, which enables binding to its primary downstream effector, the nuclear factor of activated T cells (NFAT) [53, 54]. Stimulation of the calcineurin-NFAT pathway causes an intense increase in heart size and may lead to eccentric hypertrophy. Calcineurin transgenic mice were shown to contain extensive deposits of collagen and extreme activation of the molecular hypertrophic program. Further few studies had also shown that inhibition of calcineurin-NFAT signaling had been associated with decline pathological cardiac hypertrophy in case of pressure overload stimulation or Infusion of neuroendocrine agonist infusion models of cardiac remodeling [55].

Further Studies related to the Ca2+/calmodulin-dependent kinase II (CaMKII) pathway had shown that expression and activity of CaMKII were increased in case of cardiac hypertrophy and heart failure. Various animal models also demonstrated that the level and phosphorylation of CaMKII are elevated after pressure overload in mice [56, 57]. Excessive expressed CaMKII was also reported to develop significant cardiac dilation with reduced cardiac function, cardiomyocyte enlargement and fibrosis of the myocardium. Further few studies also shown that deletion of CaMKII was associated with reduced hypertrophic fibrosis in response to pressure overload. Overall data suggest the pathological role of CaMKII in cardiac remodeling. Beside it overactivation of various pathological mediators, including Akt leads to dysfunctioning of VEGF (Vascular endothelial growth factor) which further leads to an imbalance in the process of angiogenesis, ultimately causing worsening of cardiac remodeling [58, 59]. Further over activation also elevates the action of mTOR (Mammalian Target of rapamycin), a member of the phosphatidylinositol 3-kinase-related kinase family of protein kinases and is responsible for hypertrophic mechanisms. Harmful aspects of various mediator of cardiac remodeling is summarized in **Fig. 3.**

Anti-remodeling and Associated Mechanisms of Heart: Various anti-hypertrophic mechanisms were found to counterbalance stress-induced remodeling and pathologic changes in the myocardium. Atrial natriuretic peptide (ANP) and B-type natriuretic peptide (BNP) have been reported to play a vital role in the modulation of injury and neuroendocrine stress-induced hypertrophy [60]. The natriuretic peptides are hormones mainly involved in controlling blood pressure and plasma volume status by their potent natriuretic, diuretic, and vasodilator effects. Besides these effects, natriuretic peptides were also found to antagonize hypertrophy in various pathophysiological conditions [61]. Further few studies had shown that overexpression of ANP in transgenic mice had been associated with decreased heart weight and blood pressure. Various studies have also reported that ANP receptor lacking mice shows enhanced cardiac hypertrophy. These interpretations propose an anti-hypertrophic role of ANP, which ultimately protects the development of cardiac hypertrophy independently of blood pressure. Further, the anti-hypertrophic cascades of

ANP have been found to work by the cGMP-dependent protein kinase signaling pathway (PKG). Another associated mediator, Nitric oxide (NO) has also been documented as a negative regulator of the hypertrophic response. The anti-hypertrophic effect of PKG I was found to regulate through inhibition of the calcineurin-NFAT signaling pathway [47]. Besides it despite the T-type calcium channel, the L-type calcium channels are the predominant calcium influx pathway in cardiomyocytes for initiation of contraction and communication with the ryanodine receptor in the sarco-endoplasmic reticulum (SR). However, T-type calcium channels were found to re-expressed in adult ventricular myocytes in case of pathologic hypertrophy [48]. Amazingly, few studies had shown that transgenic mice lacking T-type calcium channels are very less or not prone to pathological remodeling regardless of increased calcium influx and were found to be partially resistant to pressure overload-, isoproterenol-, and exercise-induced cardiac hypertrophy. Small GTPase Cdc42 is another signaling intermediate that may play a key role in restraining cardiac growth in response to various pathophysiological stimuli [25]. The level of activated (GTP bound) Cdc42 has been reported to increase in pressure overload or multiple agonists induced cardiac hypertrophy. Studies have shown that compared to wild mice, a transgenic mouse lacking Cdc42 develops eminent cardiac hypertrophy after pressure overload, which progresses much quickly into heart failure. Further, other anti-hypertrophic pathways are still under investigation for their pharmacological potential, including JNK, p38, MAPK, and NFAT inhibition pathways [29, 50, 53]. Various antihypertrophic mechanisms of the myocardium are summarized in **Fig. 3.**

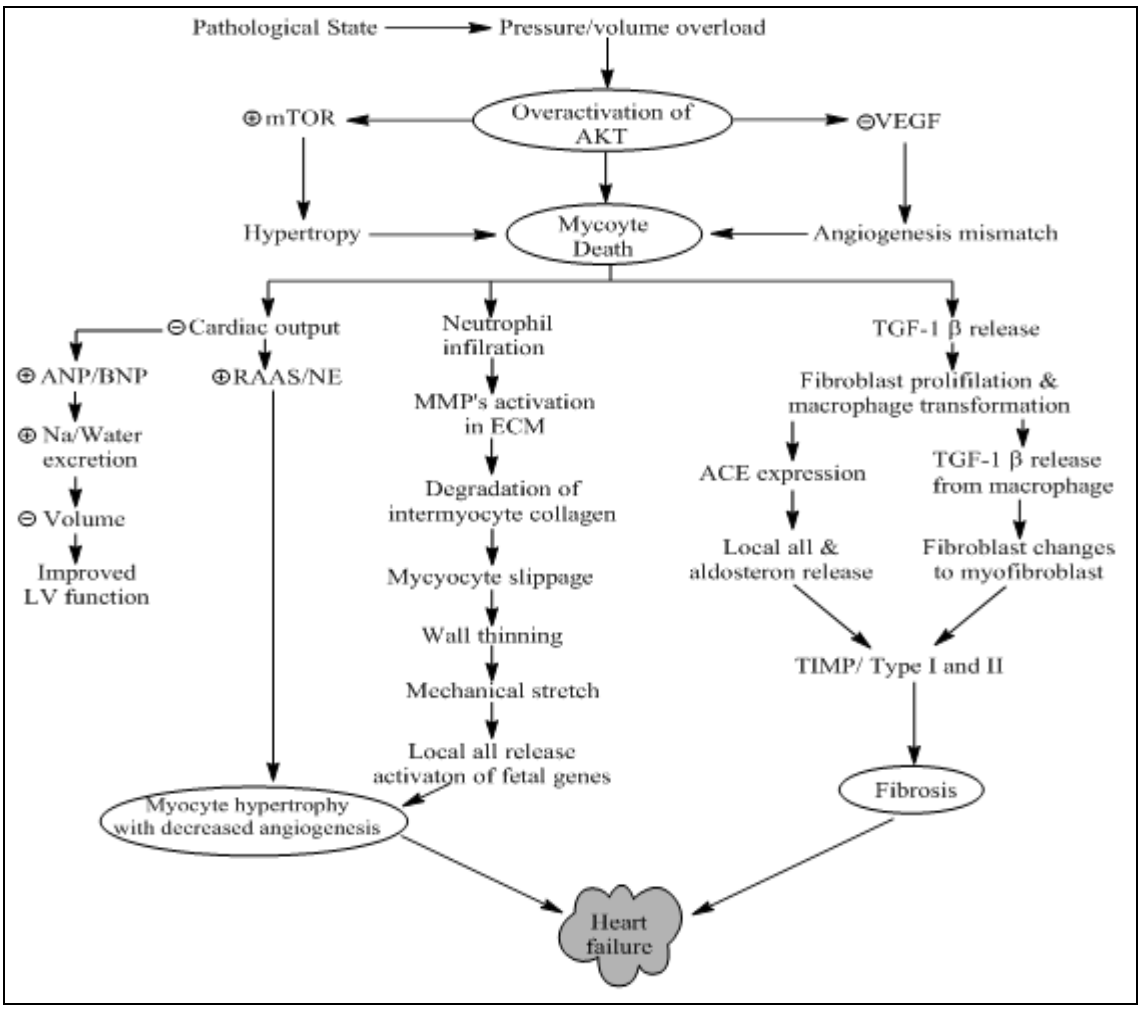

FIG. 3: HARMFUL ASPECTS OF CARDIAC REMODELING/ ANTIHYPERTROPHIC PATHWAYS. *AKT= serine/threonine kinase, mTOR= Mammalian target of rapamycin, VEGF= Vascular Endothelial Growth factor, ANP/BNP= Atrial natriuretic peptide and B-type natriuretic peptide, Na= Sodium, MMPs= Matrix metalloproteinase's, ECM= Extracellular matrix, ACE= Angiotensin converting enzyme, TIMP= Tissue Inhibitor of Metalloproteinase, LV= left Ventricle.

Pathophysiological Consequences of Cardiac Remodeling: Hypertrophy is an adaptive response to post-infarction remodeling ultimately leading to increased load, progressive dilatation and stabilization of contractile function. As a consequence of remodeling, the activation of beta 1 adrenoreceptors in the juxtaglomerular apparatus induces renin release, which further enhances the Production of Ang II [9]. This increase in Ang II production promotes the presynaptic release of Nor-adrenaline NE and blocks its reuptake. NE may augment ET-1 release, which is another stimulus for myocyte hypertrophy and stimulates the secretion of ANP. Besides activation of the RAS and adrenergic receptors, the elevated wall stresses sensed by infarcted and non-infarcted myocardium lead to local small mechanical strains which are implicated in hypertrophy [62].

Small mechanical stretches of myocytes show a tight bidirectional relationship between wall stress and myocyte hypertrophy, which resembles that between stress and hypertrophy in the intact heart. Stretch-induced hypertrophy in Cardiomyocytes mimics hemodynamic load-induced hypertrophy. These non-injurious strains are of similar magnitude to the increased wall stress from ventricular dilatation after infarction. Besides it various Growth factors, including fibroblast growth factor, epidermal growth factor, platelet-derived growth factor, insulin, and insulin-like growth factor are stimulated in response of cardiac remolding and lead to activation of various receptors including tyrosine kinase, p21 Ras and MAP kinase (extracellular regulated kinase or Jun N-terminal kinase) [51]. The activation of these all discussed mediators is the ultimate cause of transcriptional and morphological changes of Cardiomyocytes which on sustained activation can worsen the cardiac remodeling and may lead to heart failure [63].

Current Pharmacological Approaches and Their Significance in Cardiac Remodeling: Cardiac remodeling is a determinant for the clinical course of HF; till now, decelerating or reversing remodeling has been recognized as the goal of HF therapy. Various Pharmacological agents, including ACE inhibitors and beta-blockers, have been found to modify the remodeling process by altering LV end-diastolic volume and ejection [64]. These agents have been shown to reduce morbidity and mortality in various HF patients. Current therapies for heart failure have conventionally concentrated chiefly on symptomatic relief rather than on addressing underlying disease processes. Cardiac remolding is recognized as being progressive, even in the absence of clinical signs and symptoms of cardiac dysfunction. LV dysfunction and milder forms of HF play a key role in increasing the risk of sudden cardiac death [65]. Mortality associated with cardiac failure is related to an improvement in LV emptying, which would accompany peripheral vasodilation and reduced aortic impedance, and related to the deterioration of the LV remodeling with a structural reduction in chamber size. Hence, various vasodilator drugs including prazosin, diltiazem, and felodipine, cannot reduce mortality or hospitalization rate, perhaps because they fail to influence the structural remodeling process [66].

However, adding isosorbide dinitrate to hydralazinemay improves survival, as a nitrate has been shown to affect myocardial remodeling directly. Further, ACE inhibitors exert a vasodilator effect. Their beneficial role in the long-term outcome of cardiac remodeling is mainly related to neurohormonal inhibiting effects, which contribute to their favorable action on remodeling. Similarly, positive in tropic drugs can elevate hemodynamic effects, which may have adverse effects on heart survival. Milrinone, a phosphodiesterase inhibitor, is widely used for hemodynamic support in advanced HF, however oral administration of milrinone has been associated with an increase in mortality in chronic HF [14, 67]. Various other inotropic drugs, including Flosequinan, pimobendan, ibopamine, and vesnarinone, were also shown to increase mortality associated with cardiac failure.

Mechanism linked to this adverse effect is unclear; however, neurohormonal activation and ventricular arrhythmias are thought to be involved in these effects. Various ACE inhibitors, including Ramipril and Trandolapril, showed mortality benefits in early myocardial infractions, indicating ACE inhibition's beneficial effect in cardiac remodeling. Angiotensin-converting enzyme inhibition relieved symptoms and significantly improved survival in patients with HF. Further benefits of beta-blockade have been proved in multiple clinical trials of HF

[29]. Beta-blockade was shown to improve LV function consistently and delivered clinical benefits over and above those achieved on standard therapy alone. However, beta-blockade in chronic heart failure is not for short-term symptomatic relief but can improve LV function and can give long-term outcomes. Various other drugs, including Carvedilol, metoprolol, or bisoprolol, when added to standard therapy, including an ACE inhibitor, reduced mortality in large-scale studies of patients with ischemic and non-ischemic HF [68].

Further Intravenous nitroglycerin has been shown to limit infarct size, infarct expansion, infarct-related complications, and mortality for up to 1 year. Despite these positive results, the various large trails were failed to show a significant mortality benefit in patients treated with nitrates after acute myocardial infarction. Additional BG 9719, a selective A1 (Adenosine receptors) receptor antagonist, was reported to increase GFR, urine flow and sodium excretion in a dose-dependent manner which indicates the potential role of the A1 receptor in the modulation of cardiac function. Further, another molecule BG 9719 was discontinued due to its poor solubility and lack of a suitable oral formulation [9, 69]. Another A1 receptor antagonist BG 9928 has the properties of improved potency, solubility and stability than BG 9719. As per various studies, blockade of A1 receptor with BG 9928 has been associated with the protection of renal function and additive natriuretic effects without excessive potassium loss [53, 70]. However, various studies are still under investigation for the evaluation of BG 9928 in preventing heart failure. Various other pharmacological approaches are still under investigation for elevating protective aspects of cardiac remodeling and freezing harmful mechanisms linked to cardiac remodeling [71].

CONCLUSION: Reviewed literature concluded that cardiac remodeling is a response mechanism of the myocardium towards the various pathophysiological stimulus. Cardiac remodeling is initiated as a protective mechanism, as seen in the case of controlled overload-induced physiological remodeling in athletes and bodybuilders. However, sustained and high-frequency pathological stimulus leads to over-activation of mTOR-associated hypertrophy and inhibits VEGF-associated angiogenesis, which further results in mortality of cardiomyocytes, progression to fibrosis, and ultimately cardiac failure. Simultaneously Various antihypertrophic pathways are also working during the progression of cardiac remodeling; based on their action potential, they may obstruct the progression of cardiac remodeling. Several pharmacological agents are being used to freeze the remodeling process, which acts temporally and needs continuous doses. Enhancing the protective mechanism and freezing harmful mechanism of the myocardium may be the potential treatment for averting the progression of cardiac remodeling to heart failure.

ACKNOWLEDGEMENT: Nil

Funding: None

CONFLICTS OF INTEREST: The authors declare no conflict of interest, financial or otherwise.

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How to cite this article:
Dhiman S, Kumar I, Palia P and Kumar P: Cardiac remodeling: a harmful or protective mechanism of Myocardium. Int J Pharm Sci & Res 2022; 13(8): 2988-99. doi: 10.13040/IJPSR.0975-8232.13(8).2988-99.