Available online at www.scholarsresearchlibrary.com

Scholars Research Library
Central European Journal of Experimental Biology, 2024, 12 (1): 1-9
(http://scholarsresearchlibrary.com/archive.html)

ISSN: 2278-7364

Pathophysiological Basis of Cardiac Remodeling

Success Ajayi[1*], Progress Ajayi[2]

[1]*School of Life Sciences, University of Westminster, London, United Kingdom*

[2]*Afe Babalola University, Ado Ekiti, Nigeria*

[*]***Correspondence to:*** *Success Ajayi, School of Life Sciences, University of Westminster, London, United Kingdom,*

E-mail: ajayisuccess1@gmail.com

Received: *28 September, 2021, Manuscript No. CEJEB-24-43216;* ***Editor assigned:*** *01 October, 2021, Pre QC No. CEJEB-24-43216 (PQ);* ***Reviewed:*** *15 October, 2021, QC No. CEJEB-24-43216 (Q);* ***Revised:*** *01 April, 2024, Manuscript No. CEJEB-24-43216 (R);* ***Published:*** *29 April, 2024*

ABSTRACT

Cardiac remodeling is a two-phase process that is clinically manifested as the change in the size, shape, structure and function of the human heart. Its primary cause births from cardiac overload and cardiac injury. Cardiac remodeling plays a crucial role in the progression of heart failure especially when factors like oxidative stress and inflammation occur. Several investigation techniques have been unveiled in the findings about cardiac remodeling. Of these techniques, the cardiac magnetic resonance technique and the Positron Emission Tomography (PET) methods have proved helpful. Many pharmacological strategies are beginning to show promising solutions to the progression of heart failure by reverse cardiac remodeling. Of these is the recently discovered fact that Ramipril attenuates left ventricular remodeling by regulating the expression of activin A-follistatin in a rat model of heart failure.

Keywords: Cardiac remodeling, Human heart, Positron emission tomography, Pharmacological strategies

INTRODUCTION

Cardiac Remodeling (REM) is defined as a genome expression resulting in molecular, cellular and interstitial changes and manifested clinically as changes in size, shape, structure and function of the heart resulting from cardiac load or injury. In cardiology, cardiac remodeling is an aspect of the heart's cardiomyopathies. Cardiomyopathies represent a broad spectrum of diseases that affect the myocardium of the heart. These disorders could be either inherited or caused by other factors like alcohol abuse, beriberi etc. but sometimes the cause may be idiopathic.

Remodeling as a term was first used in 1982 by Hockman and Bulkley in a Myocardial Infarction (MI) model to describe the replacement of an infarct tissue with a scar tissue [1]. Janice Pfeffer was the first researcher to use the term remodeling in the current context, to describe the progressive increase of the left ventricular cavity in experimental model of myocardial infarction in rats. Cardiac remodeling has various other names: Ventricular remodeling or can sometimes be represented as 'REM'. It could be physiologic (adaptive) or pathologic in nature. As the case may be, physiologic cardiac remodeling is found in athletes in whom there are compensatory changes in the proportions and functions of the heart as regards exercise. This type of remodeling is usually reversible. In contrast, pathologic cardiac remodeling is mostly irreversible. However, the term "reverse remodeling" in cardiology implies an improvement in ventricular mechanics and function following a remote injury or pathological process.

Cardiac remodeling is usually caused either by pressure overload as in aortic stenosis and hypertension, inflammatory heart muscle disease in myocarditis, idiopathic dilated cardiomyopathy or volume overload as in valvular regurgitation. More prominently, it results after an acute myocardial infarction-especially the S-T Elevation Myocardial Infarction (STEMI) among many other causes. Myocardial infarction is the death of a segment of the heart muscle following an obstruction to its blood supply. This is usually confined to the left ventricle. These disorders have different etiologies, but they share some common pathways as regards their molecular, biochemical and mechanical events.

There are two major phases of cardiac remodeling: adaptive and maladaptive phases. In the adaptive stage, it represents a responsive mechanism to maintain cardiac output, whereas in the maladaptive stage, it results in the progression of heart failure. Several factors influence these phases of cardiac remodeling e.g. hemodynamic load, neurohormonal activation and many other which are still under investigation.

Cardiac remodeling encompasses many changes associated with progressing Heart Failure (HF) in terms of the increase in heart size, cardiac function deterioration etc. as heart failure symptoms emerge. Therapeutic interventions aimed at correcting low cardiac output or to reduce blood flow only give relief to the symptoms of heart failure and more so increase cardiac emptying but do not necessarily slow HF progression. Evidently, the use of Angiotensin Converting Enzyme (ACE) inhibitors and beta-blockade does not only slow HF but in some cases, they reverse some parameters in HF patients. Cardiac remodeling is now recognized as an important aspect of cardiovascular disease progression and is, therefore, emerging as a therapeutic target in HF of all etiologies.

The major heart structure that changes in cardiac remodeling is the myocytes. Other components include fibroblasts, the interstitium, collagen and coronary vasculature. The pathophysiology of cardiac remodeling explains that following a myocardial infarction, the infarct area dies through necrosis and thins out. Then scar formation sets in. Although, this seems to be beneficial at first because it maintains the ventricular function and cardiac output but later, the heart becomes less elliptical but more spherical.

Evaluation of cardiac remodeling is usually done through the noninvasive echocardiography which deals with the use of ultrasound waves to investigate and display the action of the heart as it beats. Also, other evaluation techniques include the use of Cardiac Magnetic Resonance imaging (CMR) based on the emission of electromagnetic waves from the body when the patient is placed in a strong magnetic field and exposed to radiofrequency radiation. Other techniques are: The use of serum biomarkers (including microRNAs) and scintigraphy-which involves the recording of the distribution of radioactive tracer in a part of the body produced by recording the flashes of light given off by a scintillator as it is struck by radiation of different intensities.

The major focus of this review is to elucidate the basic concepts of cardiac remodeling: basically, to explain its causes, reveal its role in heart failure progression as well as emphasize certain factors that play fundamental roles in the different phases of cardiac remodeling. Also, the pathophysiology, diagnostic tools for the evaluation of cardiac remodeling and their clinical implications, therapeutic interventions on cardiac remodeling process in HF and other therapies under investigation are also being taken into consideration.

LITERATURE REVIEW

Basic concepts of cardiac remodeling

The causes of cardiac remodeling can be summarized into two categories: The causes that result in cardiac injury and those that result in cardiac overload. Cardiac disorders like acute myocardial infarction, congenital heart disease (with intracardiac shunting), valvular heart disease etc. are contributing factors to cardiac injury. Also, factors that cause any form of heart strains e.g. hypertension as in pressure overload or valvular regurgitation as in volume overload potentially leads to cardiac remodeling. It is also very important to note that ventricular remodelling is characterized by ventricular hypertrophy, ventricular dilation, cardiomegaly etc. Ventricular hypertrophy has various forms such as cconcentric hypertrophy which is due to pressure overload and eccentric hypertrophy which is due to volume overload.

The mechanisms by which these two categories of factors cause cardiac remodeling are closely related as described below.

Cardiac injury

Acute Myocardial Infarction (AMI): Myocardial infarction is caused by rupture of atherosclerotic plaque leading to thrombosis in a coronary vessel lumen which leads to blood flow blockage. This implies oxygen deprivation from the myocardium. Then, necrosis is reflected by the observation of changes in morphological features of the infarcted myocardium e.g. myofibrillar contraction bands, swollen and ruptured mitochondria, destruction of cardiomyocyte membranes, microvascular destruction, hemorrhage and inflammation [2]. Other more regulated cell death occurs in myocardial infarction (although their contribution to the final infarct size is still unclear). These include: Apoptosis, autophagy and necroptosis. Apoptosis is energy-dependent and is associated with DNA disintegration but with no inflammatory response. Autophagy is a regulated mode of cell death characterized of lysosomal protein degradation and recycling. Autophagy is also considered to have a protective effect even though its role in human myocardial ischemia is less known. Necroptosis is literally derived from the words ‘necrosis’ and ‘apoptosis’. It is regulated by activation of specific receptor-interacting protein kinases.

The healing process following acute myocardial infarction is composed of three phases namely: Inflammatory, proliferative and maturation phases as shown in Figure 1. The inflammatory phase is characterized by the production of chemokines and cytokines and their corresponding infiltration by leucocytes (primarily neutrophils and macrophages). In the proliferative phase, the leucocytes release cytokines and growth factors which suppress inflammatory mediators’ activity and promote angiogenesis, fibroblast growth and production of extracellular matrix proteins. This actions at the proliferative phase all contributes to tissue granulation. As regards the maturation phase, fibroblasts and vascular cells undergo apoptosis and a mature collagen scar is formed.

Since the stiff scar formed following myocardial infarction is composed mainly of collagen, the scar is far less contractile than the surrounding myocardium; when it is not sufficiently firm, the infarcted tissue is prone to dilatation and/or rupture.

When a segment of the myocardial wall becomes stiff, assuming constant internal volume, the remaining myocardium is stretched with greater force during diastole. In addition, in order to maintain cardiac output, the remaining healthy tissue must generate more force to compensate for the scar. This makes the presence of stiff scars in myocardium a sort of analogue of elevated systolic and diastolic pressure.

Furthermore, the post-Myocardial Infarction (MI) consequences include the stimulation of the Renin-Angiotensin-Aldosterone System (RAAS) and decrease in the amount of Tissue Inhibitory Matrix Metalloproteinases (TIMPs). These two actions lead to the activation of Matrix Metalloproteinases (MMPs)-which are a family of proteolytic enzymes usually inactive in the normal heart. Then, the MMPs degrades the extracellular proteins within the myocardium and mediate cellular mechanisms of infarct expansion, left ventricular dilatation and myocardial thinning. The aftermath of these effects is an indication of heart failure.

Also, the hyperinnervation of non-infarcted myocardium have been observed after a myocardial infarction. It is possible that these changes are mediated largely by similar stretch-sensing mechanisms which come to play as a result of pressure overload as seen in hypertension with the same consequences of their imbalance. Tomek et al. says as at now to our knowledge there is no study researching the role of post-infarction interstitial hyperinnervation in maintaining contractility, but the role of matrix metalloproteinases and their inhibition after MI has been studied in animal models. The results are largely consistent with the role of collagen dynamics in hypertension, where inhibition of degradation *via* Matrix Metalloproteinase (MMP) inhibition attenuates left ventricular dilatation; this effect is not entirely due to the acute healing phase, but has a role in the late healing phase as well.

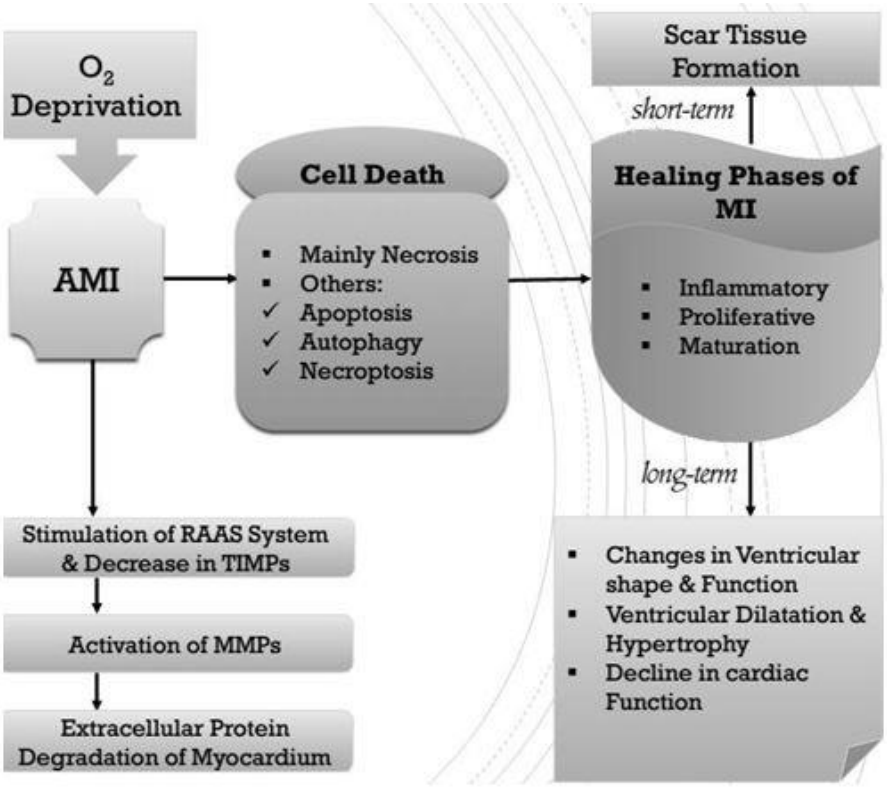

Figure 1: Pathophysiology of post-MI cardiac remodeling.

Cardiac overload

Pressure overload in hypertension: Hypertension is a multifactor disease characterized by chronic elevation in blood pressure to levels equal to or above 140 mmHg Systolic Blood Pressure (SBP) and above 90 mmHg of Diastolic Blood Pressure (DBP). Hypertension is the main risk factor for cardiovascular diseases being epidemiologically closely associated with metabolic diseases such as obesity and diabetes.

Its development is attributed to multifactorial and unknown factors e.g. the association of several pathophysiological stimuli (e.g., obesity and diabetes) with environmental factors (e.g., diet, lifestyle, tobacco and alcohol abuse) and genetic background with hereditability estimated at 15%-40% [3,4].

In hypertension, there is a buildup of pressure overload that causes cardiac pathological hypertrophy which is one of the main phenotype adaptations to hypertension. Complex molecular signaling marks this process, which is transcript to an altered cardiac proteome. This pathologic hypertrophy is often marked by dysfunction within cardiac function, which may later progress into HF.

The main alterations in the heart and myocyte morphology due to pathological hypertrophy in hypertension include: Increased myocyte and overall heart size, increased apoptosis, increased fibrosis, decreased Free Fatty Acid (FFA) oxidation with a shift to glucose metabolism, contractile dysfunction and altered gene expression which is associated with the development of cardiac dysfunction rather than cardiac improvement.

Increase in myocyte size, is triggered by several events, including increased functional load on myocyte, activation of signaling pathways and gene expression, upregulation of protein synthesis and formation of novel sarcomeric units [5]. Moreover, this process seems to be triggered by a mechano-sensing mechanism in cardiac myocytes through stretch-sensitive ion channels, growth factor receptors and G-protein-coupled receptors, linking stress and pressure overload stimulus to gene regulation and protein synthesis (Figure 2).

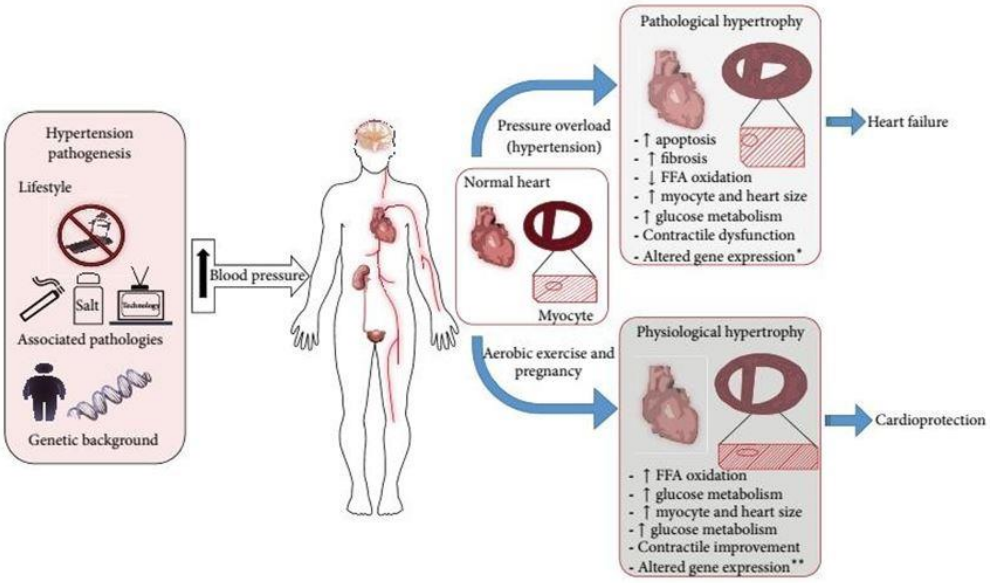

Figure 2: Comparison of pathologic hypertrophy seen in hypertension with physiologic hypertrophy.

DISCUSSION

Cardiac remodeling and its role in heart failure progression

Heart Failure (HF) is a clinical syndrome caused by structural and functional defects in myocardium resulting in impairment of ventricular filling or the ejection of blood [6]. Heart Failure (HF) is a worldwide health problem that affects approximately 26 million individuals. Cardiac remodeling is generally an adverse sign and is linked to HF progression. Patients with major remodeling demonstrate progressive worsening of cardiac function and it may underlie a sizeable proportion of cardiovascular morbidity and mortality. Mechanisms other than remodeling can, however, also influence the course of heart disease and disease progression may occur in other ways in the absence of cardiac remodeling.

Cardiac remodeling involves both adaptive and maladaptive phases of development. In the initial stage, it represents an adaptive response to maintain cardiac function, whereas in the late stage, it results in the progression of heart failure. Increments in load, such as those seen in mitral insufficiency, modulate remodeling of the ventricle to maintain forward flow, but often after cardiac injury (such as AMI), continued remodeling may not be necessary to maintain the integrity of the circulation. Under such circumstances, remodeling may be viewed as an adverse phenomenon that leads to progressive decompensation.

Progressive remodeling, irrespective of the criteria used to measure it, can always be considered deleterious and is associated with a poor prognosis. There are no data to indicate when the transition from possible adaptive to maladaptive remodeling occurs or how this might be identified in patients. The occurrence of such a transition and its time course may be expected to vary greatly. However, once established beyond a certain phase, it is likely that remodeling actually contributes to HF progression (Figure 3).

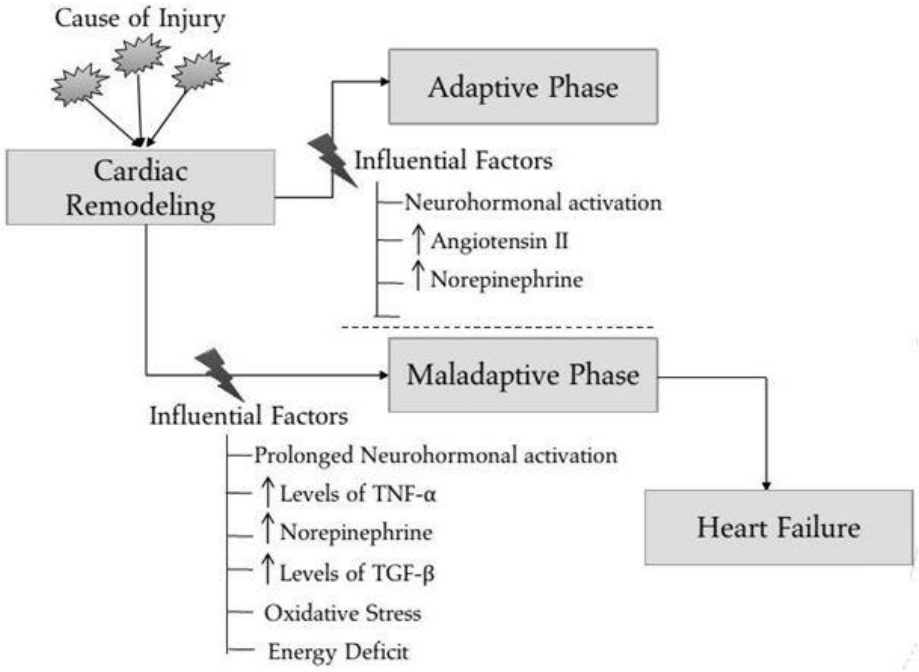

Figure 3: The stages of cardiac remodeling and its role in heart failure progression.

Oxidative stress appears to be the main factor that induces transition of cardiac hypertrophy (a characteristic of cardiac remodeling) to heart failure as a consequence of alterations in signal transduction, dysfunction of the sarcolemma and sarcoplasmic reticulum, impairment of calcium handling, increases in cardiac fibrosis and progressive loss of cardiomyocytes.

The role of oxidative stress in cardiac remodeling

Oxidative stress is defined as an excessive production of Reactive Oxygen Species (ROS) juxtaposed with the antioxidant defense system. Many experimental and clinical studies have demonstrated an increased production of ROS in the failing heart [7]. With the persistence of some factors e.g. prolonged neurohormonal activation, increased levels of Tumor Necrosis Factors (TNF-α and TNF-β) etc. at the maladaptive phase of cardiac remodeling, oxidative stress comes into play and aids the progression of cardiac remodeling into heart failure.

In physiologic conditions, a small amount of ROS is produced in the mitochondrial respiratory chain; this small quantity of superoxide anion (O_2^-) is detoxified by the antioxidant system. Particularly in conditions in which oxygen availability is decreased, mitochondrial production of ROS is enhanced. ROS have four main sources: Interaction of leukocytes with cytokines; abnormalities in mitochondrial respiratory chain; increased NAD(P)H oxidase reactivity; and increased xanthine oxidase function.

However, in HF, mitochondria release O_2^- in significant quantities in the presence of NADH. During the development of HF:

- The levels of different hormones, such as angiotensin II and endothelin-1, are elevated in addition to tumor growth factor-α, which increase NAD(P)H oxidase activity and lead to ROS production [8].
- Xanthine oxidase enzyme expression and function are also elevated, representing an additional source of ROS. This correlates to experimental studies that have demonstrated that allopurinol, a xanthine oxidase inhibitor is used in the treatment of HF in some animal models.

Also, the decreased expression of V1 myosin and L-type calcium channels with other inflammatory immune response after myocardial infarction leads to increased oxidative stress of the heart, proliferation of fibroblasts, activation of metalloproteinases and induction of apoptosis [9].

Influences on cardiac remodeling

Cardiac remodeling has been known to have two basic phases: An initial stage where it is known to compensate for any cardiac injury or overload for the proper maintenance of heart function and a late stage where it could progress to heart failure. At each of these stages, some elements and factors exert certain influences on the cardiac injury or overload which determines the outcome of cardiac remodeling either as an adaptive or maladaptive mechanism.

Influences at the adaptive stage of remodeling

Hemodynamic load: Changes occur in the wall stress and tension of the cardiac myocardium following a cardiac injury. Studies of global Left Ventricular (LV) chamber volumes and muscle mass show that early LV dilation in patients with anterior wall myocardial infarction may continue progressively and unabated; global compensatory (reactive) ventricular hypertrophy appears to be a delayed and limited adaptation during the first year.

If cardiac dilation persists without hypertrophy, myocardial wall stress is increased. A number of mechanisms may be stimulated by increased wall stress and this may lead to further dilation of the heart. If adequate therapy is used to reduce this ventricular dilation, although the wall stress is reduced, a favorable neurohormonal pattern is promoted. This process progresses towards overt chronic heart failure [10].

Neurohormonal activation: Neurohormonal activation is known to mediate compensatory changes in response to falling cardiac output, but it is also a major component of disease progression to HF and of the remodeling process.

Influences at the maladaptive stage of remodeling

Reactive oxygen species and neurohormonal stimulation: ROS and neurohormonal stimulation can activate several protein kinases and transcription factors and depending on the stimuli, can lead to different patterns of cardiac hypertrophy. Low levels of H_2O_2 are associated with an increase in the activity of Mitogen-Activated Protein Kinases (MAPK). MAPK cascades are complex multiple levels of kinases that include a phosphorylation-based amplification network normally activated by a membrane G protein.

MAPK cascades are classified into three major categories: p38 kinases; c-Jun N-terminal kinases; and Extracellular Regulated Kinases (ERK). Experimental studies have shown that transgenic mice overexpressing MEK-1 and ERK ½ activation developed a concentric hypertrophy pattern, showing increased myocytes width (sarcomeres assembled in parallels) similar to the pattern of hypertrophy due to pressure overload, but without fibrosis [11]. Other studies involving mice overexpressing activated mutant ERK5, related to the MEK5-ERK5 category of MAPK, have reported eccentric hypertrophy, exhibiting ventricular dilation and internal radius increasing (sarcomeres assembled in series), similar to the pattern of volume overload- induced hypertrophy, but again with no sign of fibrosis.

Oxidative stress and neurohormonal activation: This relationship causes Ca^{2+} transport dysfunction. The two major structures that modulate the intracellular concentration of Ca^{2+}, the Sarcolemma (SL) and the Sarcoplasmic Reticulum (SR), also exhibit alterations in cardiac remodeling. In physiological conditions, the excitation contraction process is activated after a small quantity of Ca^{2+} influx through SL, which in turn stimulates a release of Ca^{2+} from the SR. In the relaxation phase, it is estimated that approximately 80% of the free cytoplasmic Ca^{2+} is accumulated in the SR [12]. In cardiac remodeling, modifications in the expression of the sarcolemma Na^+Ca^{2+} exchanger (which uses the influx of Na^+ to remove the intracellular Ca^{2+}) and the SR Ca^{2+}-ATPase (SERCA) (which is responsible for Ca^{2+} sequestration during diastolic phase) have been reported.

In this condition, messenger RNA and proteins levels of SERCA are reduced, whereas that of the Na^+Ca^{2+} exchanger are elevated or unaltered [13]. Decreased levels of SERCA reduce Ca^{2+} diastolic sequestration, leading to an abnormal force-frequency relationship and a decreased developed tension. The elevated expression and function of the Na^+Ca^{2+} exchanger can lead to a large amount of Na^+ influx, which is further associated with potential membrane depolarization that can generate amplified arrhythmogenesis. The expression of SR phospholamban protein (a SERCA inhibitor and decreases Ca^{2+} sequestration) is depressed, representing an adaptive mechanism to compensate for SERCA dysfunction in HF.

In cardiac remodeling, both the sympathetic nervous system and the Renin-Angiotensin System (RAS) are activated and different studies have demonstrated their relationship with dysfunction of intracellular Ca^{2+} handling. ROS also modifies the proteins involved in excitation-contraction coupling, and there is evidence that ROS can suppress L-type Ca^{2+} channels, causing oxidative interaction with Ca^{2+} ATPase in the SR to inhibit Ca^{2+} uptake and enhance the probability of opening ryanodine receptors.

Cardiovascular changes in cardiac remodeling

Components of change in cardiac remodeling: The components of cardiac remodeling refer to the body cells or tissues that are involved or affected by the whole process of cardiac remodeling. These include:

Cardiac myocytes: Myocytes and other cardiac cell types are believed to be fundamentally involved in the remodeling process. The myocytes of all cardiovascular cells are given much attention because of their contractile activity and numeric contribution to the heart mass. As the result of an insult, myocyte numbers decrease and surviving myocytes become elongated or hypertrophied as part of an initial compensatory process to maintain stroke volume after the loss of contractile tissue. The thickness of the ventricular wall also increases [14]. Altered loading conditions stretch cell membranes and may play a role in inducing the expression of hypertrophy-associated genes. In cardiac myocytes, this may lead to the synthesis of new contractile proteins and the assembly of new sarcomeres. It is thought that the pattern in which these are laid down determines whether the cardiac myocytes elongate or increase their diameter [15]. Increased wall stress may precipitate energy imbalance and ischemia, which is one of the major determinants of myocardial oxygen demand. This is thought to lead to a vicious cycle of increased wall stress and wall thickness and further energy imbalance and ischemia.

Fibroblasts: Both fibroblasts and endothelial cells are activated in response to an ischemic insult. In human and animal models, fibroblast stimulation increases collagen synthesis and causes fibrosis of both the infarcted and non-infarcted regions of the ventricle, thus contributing to remodeling. The relative contribution of the interstitium to the remodeling process is, however, not clear.

Collagen: The myocardium consists of myocytes tethered and supported by a connective tissue network composed largely of fibrillar collagen, which is synthesized and degraded by interstitial fibroblasts. Myocardial collagenase is thought to be an important proenzyme present in the inactive form in the ventricle [16]. Its activation after myocardial injury contributes to an increase in chamber dimension in response to the distending pressure that is thought to be a possible cause of myocyte slippage, which some consider one contributor to chamber remodeling.

Structural and functional changes in cardiac remodeling

Since cardiac remodeling represents both an adaptive and maladaptive phenomenon, it usually results in several changes in the heart function and structure. Moreover, these changes are implicated by the basic changes that occur in the molecular, cellular, interstitial and microvasculature entities of the heart. Major events of change in the cardiomyocyte include hypertrophy and cell death. For the interstitium, fibrosis and inflammation occur and for the microvasculature, vascular wall thickening and decreased capillarization are the major events of change.

Gross changes: As the heart remodels, its geometry changes; it becomes less elliptical and more spherical. There are also changes in ventricular mass, composition and volume, all of which may adversely affect cardiac function [17]. Marked increase in volume results from increased circumference and sphericity. The late change in circumference is due to lengthening of contractile tissue rather than further expansion of the infarcted, noncontractile segment. The increased sphericity results from a rounding out of the sharp abnormalities in contour at the margins of the infarct.

Functional changes: This cellular rearrangement of the ventricular wall is associated with maintained or improved cardiac output but with significantly increased LV volumes. The magnitude of remodeling changes observed relates roughly to infarct size. After one-month, large infarcts provoke greater dilation and greater increases in systolic and diastolic stress than small infarcts. In progressive post-infarction dilation, the end-systolic volume index increases progressively and ejection fraction declines. These are important predictors of mortality.

Diagnostic tools and their clinical implications

At present, echocardiography remains the predominant clinically applicable noninvasive test of choice, based on broader availability, whereas alternative modalities, such as radionuclide imaging and Cardiac Magnetic Resonance (CMR), also play an important role, with each modality offering advantages and disadvantages. More recently, better techniques such as the use of single photon emission tomography and positron-emission tomography are used for the investigation of the molecular processes that occur in the cardiomyocytes after a myocardial infarction a function that could not be achieved by other previous techniques.

Echocardiography: Echocardiography can be performed in mainly 2 dimensional views: The 2D and 3D. 2D echocardiography is a widely-established means of evaluating LV remodeling. It is commonly assessible and is not associated with any radiation exposure. This technique can be performed in nearly all patients no matter the degree of illness. However, a prominent down-side with this technique is that the estimates of LV volumes obtained from 2D images are subject to variability and error imposed by selection of the imaging plane, inaccuracies in identifying the endocardial border, geometric assumptions underlying the volumetric calculations and beat-to-beat variation in LV volume and function. Kober et al. using the Simpson method when compared with *in vitro* canine measurements demonstrated the accuracy of echocardiographic LV volumes estimates. Subsequently, harmonic imaging and contrast echocardiography have improved 2D echocardiographic image quality [18]. In the more recent times, real-time 3D echocardiography has emerged as a clinically feasible method for quantifying ventricular volume and mass. 3D echocardiographic quantification of ventricular volumes and ejection fraction can be performed rapidly and avoids the geometric assumptions and problems of image plane position that are associated with 2D echocardiography.

3D echocardiography has superior accuracy and reproducibility for evaluation of ventricular chambers compared with 2D echocardiography and several studies have observed that 3D echocardiographic assessments of ventricular volumes, mass and ejection fraction correlate favorably with CMR.

Cardiac magnetic resonance: CMR is a 3D imaging technique producing images with high spatial and temporal resolution. The generation of thin, short-axis imaging slices with full ventricular coverage results in truly tomographic imaging without the limitation of geometric assumptions associated with 2D non-tomographic imaging techniques. In addition, contemporary imaging sequences generate sharp contrast between the bright blood pool and dark myocardium, which results in accurate measurements of volume, mass and wall thickness. A number of investigations have demonstrated strong correlations for LVEFs and volumes measured by CMR versus contrast angiography or echocardiography.

CMR is now considered the reference for noninvasive measurements of functional and volumetric parameters. In addition, the superior reproducibility of these measurements with CMR facilitates application of CMR as a research tool for clinical investigation. For example, the sample size needed to demonstrate a given change in volume or mass with statistical confidence is substantially reduced with CMR compared with 2D echocardiography, a factor that may offset the increased cost of CMR by virtue of the savings from studying fewer patients per trial [19]. Beyond geometric measurements, contrast enhanced CMR, with assessment of Late Gadolinium Enhancement (LGE), has demonstrated the ability to predict patient risk of adverse remodeling post-MI. Due to the high spatial resolution, LGE, a marker of myocardial scarring, can identify acute and chronic MI with high accuracy and reproducibility. Areas of LGE can be planimetered and the amount quantified and expressed as a percentage of the total LV mass or a percentage of the LV wall segment involved. This technique can also demonstrate microvascular obstruction, as evidenced by a central dark zone, surrounded by bright enhancement of the infarcted core, a finding that marks a greater risk of adverse LV remodeling post-MI.

Treatments and management of cardiac remodeling

Pharmacologic treatment of cardiac remodeling: Treating cardiac remodeling by the use of pharmacologic products is often classified by three strategies:

- Consolidated strategies
- Promising strategies
- Potential strategies

Consolidated strategies: The use of Renin-Angiotensin-Aldosterone System (RAAS) inhibitors e.g. angiotensin-converting enzyme inhibitors, beta blockers and aldosterone antagonists have been consistently shown to decrease remodeling in animal models. These findings have been validated in clinical trials and these drugs are currently indicated for patients with ejection fraction of <40%.

Promising strategies: LCZ696, a product which combines a valsartan molecule (angiotensin II receptor antagonist) and sacubitril (inhibitor of neprilysin, which metabolizes natriuretic peptides, urodilatin, bradykinin and adrenomedullin) shows promising effective treatment for cardiac remodeling as revealed by several experimental studies e.g.

- Studies that showed the attenuation of ventricular cavity dilation and myocardial fibrosis after MI through the use of LCZ696.
- Clinical trial study the PARADIGM-HF trial which was conducted on more than 8,000 patients with chronic symptomatic heart failure with reduced ejection fraction (NYHA class II-IV). These patients were randomly given LCZ696 and after a follow-up of about 27 months, it was found out that the LCZ696 showed lower all-cause mortality rate, lower cardiovascular mortality, and fewer hospitalizations for cardiac failure.

Potential strategies: With respect to potential therapies, the main targets are pathophysiological mechanisms previously described, especially in experimental studies. Cell death has been one of the main targets investigated. Previous studies have shown that cyclosporine and neuregulin-1 attenuate apoptosis; also, necrostatin-1 attenuates apoptosis *via* inhibition of caspase-8 and reduces necrosis *via* blockage of calpain activity. Modulation of chaperones and the ubiquitin-proteasome system (hence modulating protein degradation) would also lead to greater survival. Fibrosis has also been an attractive target for therapeutic interventions. Inhibition of thrombospondin-1 and galectin-3 is associated with a decrease of collagen content [20]. The same effect was reported after administration of torsemide and metformin. In addition, administration of CXL-1020, a nitroxyl donor, enhanced the sensitivity of contractile proteins to calcium, with consequent functional improvement and attenuation of hypertrophy. Also, modulation of inflammatory process, including macrophages, T lymphocytes and cytokines has been investigated in different models, with promising results. Continuous investigation of new compounds for the attenuation of cardiac remodeling/dysfunction has been made and a number of potential strategies are currently available.

CONCLUSION

From this review, it has been shown that cardiac remodeling prior to cardiac injury or increased cardiac load leads to various changes in the heart structure, size, shape and function which eventually indicate ventricular dysfunction as it progresses to heart failure. Although cardiac remodeling has an adaptive phase, but in-depth knowledge on the mechanisms involved in this process at the molecular level is highly recommended in further researches so that more strategies of treatment and management can be unraveled. This can be achieved by ensuring the availability of more sophisticated techniques e.g. Positron Emission Tomography (PET), Single Photon Emission Tomography (SPECT) etc. because these techniques have been found to enable the investigation of molecular changes that occur in cardiac injuries and overload.

REFERENCES

1. Hochman, J. S., and Bulkley, B. H., Expansion of acute myocardial infarction: An experimental study. *Circulation*, **1982**. 65(7): p. 1446-1450.
2. Curley, D., et al., Molecular imaging of cardiac remodelling after myocardial infarction. *Basic Research in Cardiology*, **2018**. 113: p. 1-8.
3. Newton-Cheh, C., et al., Genome-wide association study identifies eight loci associated with blood pressure. *Nature Genetics*, **2009**. 41(6): p. 666-676.
4. Delles, C., et al., Genetics of hypertension: From experimental animals to humans. *Biochimica et Biophysica Acta*, **2010**. 1802(12): p. 1299-1308.
5. Bernardo, B. C., et al., Molecular distinction between physiological and pathological cardiac hypertrophy: Experimental findings and therapeutic strategies. *Pharmacology and Therapeutics*, **2010**. 128(1): p. 191-227.
6. Inamdar, A. A., and Inamdar, A. C., Heart failure: Diagnosis, management and utilization. *Journal of Clinical Medicine*, **2016**. 5(7): p. 62.
7. Hill, M. F., Singal, P. K., Antioxidant and oxidative stress changes during heart failure subsequent to myocardial infarction in rats. *The American Journal of Pathology*, **1996**. 148(1): p. 291.
8. Doughan, A. K., Harrison, D. G., and Dikalov, S. I., Molecular mechanisms of angiotensin II-mediated mitochondrial dysfunction: Linking mitochondrial oxidative damage and vascular endothelial dysfunction. *Circulation Research*, **2008**. 102(4): p. 488-496.
9. Azevedo, P. S., et al., Cardiac remodeling: Concepts, clinical impact, pathophysiological mechanisms and pharmacologic treatment. *Arquivos Brasileiros de Cardiologia*, **2015**. 106: p. 62-69.
10. Grossman, W., Jones, D., and Mclaurin, L. P., Wall stress and patterns of hypertrophy in the human left ventricle. *The Journal of Clinical Investigation*, **1975**. 56(1): p. 56-64.
11. Bueno, O. F., et al., The MEK1-ERK1/2 signaling pathway promotes compensated cardiac hypertrophy in transgenic mice. *The EMBO Journal*, **2000**. 19(23): p. 6341-6350.
12. Babick, A. P., and Dhalla, N. S., Role of subcellular remodeling in cardiac dysfunction due to congestive heart failure. *Medical Principles and Practice*, **2007**. 16(2): p. 81-89.
13. Hasenfuss, G., et al., Relationship between Na^{+}-Ca^{2+}-exchanger protein levels and diastolic function of failing human myocardium. *Circulation*, **1999**. 99(5): p. 641-648.
14. Anversa, P., Olivetti, G., and Capasso, J. M., Cellular basis of ventricular remodeling after myocardial infarction. *The American Journal of Cardiology*, **1991**. 68(14): p. 7-16.
15. Francis, G. S., and McDonald, K. M., Left ventricular hypertrophy: An initial response to myocardial injury. *The American Journal of Cardiology*, **1992**. 69(18): p. 3-9.
16. Cleutjens, J. P., et al., Regulation of collagen degradation in the rat myocardium after infarction. *Journal of Molecular and Cellular Cardiology*, **1995**. 27(6): p. 1281-1292.
17. Gaudron, P., et al., Progressive left ventricular dysfunction and remodeling after myocardial infarction. Potential mechanisms and early predictors. *Circulation*, **1993**. 87(3): p. 755-763.
18. Kasprzak, J. D., et al., Comparison of native and contrast-enhanced harmonic echocardiography for visualization of left ventricular endocardial border. *The American Journal of Cardiology*, **1999**. 83(2): p. 211-217.
19. Bellenger, N. G., et al., Comparison of techniques for the measurement of left ventricular function following cardiac transplantation: Ventricular function. *Journal of Cardiovascular Magnetic Resonance*, **2002**. 4(2): p. 255-263.
20. de Boer, R. A., et al., Galectin-3: A modifiable risk factor in heart failure. *Cardiovascular Drugs and Therapy*, **2014**. 28: p. 237-246.