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REVIEW ARTICLE OPEN ACCESS

A REVIEW ON CARDIAC REMODELLING

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Abstract

Heart failure (HF) is a worldwide health problem that affects approximately 26 million individuals. It is known that heart disease progresses to HF, and there is a link between cardiac remodelling and the development of HF. The term "remodelling" was used for the first time in 1982 by Hockman and Buckey, in a myocardial infarction (MI) model. Cardiac remodelling refers to changes in the size, shape, structure, and function of the heart. This can happen as a result of exercise (physiological remodeling) or after injury to the heart muscle (pathological remodeling).{3} The injury is typically due to myocardial infarction. Chronic hypertension, congenital heart disease with intracardiac shunting, and valvular heart disease may also lead to remodelling. Between the physiological and pathological remodelling, the physiological remodelling is reversible and the pathological remodeling is irreversible. Cardiac remodelling is considered to be not only an adaptive event but also a maladaptive phenomenon. In the acute phase of a myocardial stress, cardiac remodelling acts as an adaptive response that enables the heart to maintain cardiac output; however, after the prolonged stressful stimulus, this continuous process leads to progressive decompensation. The cardiac myocyte is the major cell involved in remodeling. Fibroblasts, collagen, the interstitium, and the coronary vessels to a lesser extent, also play a role. The most used methods to detect these changes are echocardiography, ventriculography, and nuclear magnetic resonance. Several markers may indicate a remodelling process, including changes in the expression of myosin heavy chain isoforms, with an increase in alpha- and a decrease in beta-myosin heavy chain, increased expression of GLUT-1, alpha-actin, natriuretic peptide, galectin, caveolin, neuronal nitric oxide synthase, angiotensin-converting enzyme, a decrease in GLUT-4, SERCA2a, and a shift from glucose to fatty acid oxidation.Medications may attenuate remodelling , Angiotensin-converting enzyme (ACE) inhibitors, Beta blockers (Carvedilol), may actually reverse the remodelling process by reducing left ventricular volumes and improving systolic function.

Keywords: Cardiac remodelling, Heart failure, Angiotensin –converting enzyme, Cardiac output, Chronic hypertension.

INTRODUCTION

The term "remodeling" was used for the first time in 1982 by Hockman and Buckey, in a myocardial infarction (MI) model.{1} In cardiology, ventricular remodeling (or cardiac remodeling){2} refers to changes in the size, shape, structure, and function of the heart. This can happen as a result of exercise (physiological remodeling) or after injury to the heart muscle (pathological remodeling).{3} The injury is typically due to myocardial infarction. Chronic hypertension, congenital heart disease with intracardiac shunting, and valvular heart disease may also lead to remodeling. Between the physiological and pathological remodeling, the physiological remodeling is reversible and the pathological remodeling is irreversible.{4,5,6}. Cardiac remodeling is generally accepted as a determinant as a clinical course of heart failure(HF).Defined as genome expression resulting in molecular, cellular and interstitial changes and manifested clinically change in size, shape or function of the heart resulting from cardiac load or injury, cardiac remodeling is influenced by hemodynamic load, Neuro hormonal activation and other factors still under investigation.{7} Cardiac remodeling is considered to be not only an adaptive event but also a maladaptive phenomenon. In the acute phase of a myocardial stress, cardiac remodeling acts as an adaptive response that enables the heart to maintain cardiac output; however, after the prolonged stressful stimulus, this continuous process leads to progressive decompensation.{8} As a result of this phenomenon, the heart develops cellular changes such as myocyte hypertrophy{9}, necrosis{10}, apoptosis{11,12}, fibroblast proliferation{13}, increased fibrillarcollagen{14}and fibrosis{15}.Cardiac remodeling may include ventricular hypertrophy, ventricular dilation, cardiomegaly, and other changes. The myocytes is the major cardiac cell involved in the remodeling process.{16}Patients with major remodeling demonstrate progressive worsening of cardiac function, and it may underlie sizeable proportion of cardiovascular morbidity and mortality.{17}

EPIDEMIOLOGY

Heart failure (HF) is a worldwide health problem that affects approximately 26 million individuals. It is known that heart disease progresses to HF, and there is a link between cardiac remodeling and the development of HF.[18] The burden of heart failure(HF) represent the inability of the heart to respond to circulatory demand of the organism. The main causes of HF are hypertension ischemic and valvular injuries whereas toxic, metabolic or genetic origins are less common. The prevalence of the HF is important and to more then 20 million people worldwide are estimated to suffer from HF. In the united kingdom, Stewart have an estimated that the annual direct cost of the HF in year 2000 about 1.9% of total expenditure of the national health service.[19,20]

Pathophysiology

- The cardiac myocyte is the major cell involved in remodeling. Fibroblasts, collagen, the interstitium, and the coronary vessels to a lesser extent, also play a role. The remodeling process frequently include increase myocardial mass. The heart can respond to environment stimuli by growth or shrinkage with a dynamic range of the least 100 percent. Myocardial hypertrophy is the most properly defined increase cardio myocyte size which might be occur with or without the increase in overall myocardial mass; however term hypertrophy also been used to donate increased myocardial mass and wall thickness.[21,22]
- Physiologic remodeling is compensatory change in dimensions and function of the heart in the response physiologic stimuli such exercise and pregnancy. This type of the remodeling seen in athletes and has been called athletes heart. The pathologic remodeling may occurs with pressure overload, volume overload and other cardiac injury.[23]

CLINICAL CHARACTERIZATION

The clinical diagnosis of remodeling is based on the detection of morphological changes – changes in the cavity diameter, mass (hypertrophy and atrophy), geometry (heart wall thickness and shape), areas of scar after MI, fibrosis and inflammatory infiltrate (e.g in myocarditis).[24] The most used methods to detect these changes are echocardiography, ventriculography, and nuclear magnetic resonance.[25] One example of clinical detection of remodeling occurs in the acute and chronic phase of MI. Another diagnostic method, still not used in routine clinical practice, consists of the detection of cell markers, which is based on the fact that cardiac remodeling involves the re expression of fetal genes. Several markers may indicate a remodeling process, including changes in the expression of myosin heavy chain isoforms, with an increase in alpha- and a decrease in beta-myosin heavy chain, increased expression of GLUT-1, alpha-actin, natriuretic peptide, galectin, caveolin, neuronal nitric oxide synthase, angiotensin-converting enzyme, a decrease in GLUT-4, SERCA2a, and a shift from glucose to fatty acid oxidation.[26,28]

FUNTIONAL CHANGES ASSOCIATED WITH CARDIAC REMODELLING

- Left ventricular enlargement in patients with anterior myocardial infraction. Marked increase in a volume results from increased circumference and the sphericity.
- **Gross changes to the heart:** As the heart remodel, geometry change; it becomes less elliptical and more spherical. There are also changes ventricular mass, compositions and volume; all of that may adversely affect cardiac function.[29]
- **Cellular and molecular changes in the remodeling:** remodeling included the cellular changes like myocyte hypertrophy, necrosis ,apoptosis, fibrosis, increased febrile collagen and fibroblast proliferation.[30]

INFLUENCES ON CARDIAC REMODELING

Changes in Hemodynamic Load:

Studies of global LV chamber volumes and muscle mass show that early LV dilation in patients with anterior wall MI may continue progressively and unabated; global compensatory (reactive) ventricular hypertrophy appears to be a delayed and limited adaptation during the first year.[31] As a result of progressive ventricular dilation and insufficient development of reactive ventricular hypertrophy, global LV wall tension and stresses increase considerably during this period.[32] The importance of remodeling as a pathogenic mechanism is unclear, and the factors leading to remodeling may be the major determinants of HF prognosis rather than ventricular dilation itself. 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. Without therapy to reduce ventricular dilation, decrease wall stress and promote a favorable neurohormonal pattern, this process progresses towards overt chronic HF.[33]

Neurohormonal Activation in HF:

- Neurohormonal activation in HF is known to mediate compensatory changes in response to falling cardiac output, but it is also a major component of disease progression and of the remodeling process.[34,35-39]
- Plasma norepinephrine levels, reflecting increased adrenergic activation, are elevated in HF patients[40,41]and relate to prognosis.[42] Higher levels of circulating plasma norepinephrine correlate with a poorer long-term prognosis.[43,44,45] Increased plasma or tissue levels of other neurohormones also occur in patients with LV dysfunction and in asymptomatic patients post-MI without HF, with activation increasing further as overt HF ensues.[46] Most recently, neurohormonal activation was shown to decrease progressively post-MI in patients with a good prognosis.[47]
- Using measures of atrial natriuretic peptide (ANP), aldosterone, norepinephrine and plasma renin, asymptomatic patients who experienced an event within three months of MI had markedly elevated neurohormonal levels a mean of 10 days after infarction.[47] In contrast, post-MI patients who were without cardiovascular events during the 38-month mean follow-up of the study had lower neurohormonal levels that decreased further over time.[47]
- In cell culture, angiotensin II increases DNA synthesis in myocardial fibroblasts and increases protein synthesis in both fibroblasts and myocytes.[48] It appears to be an important mediator of the cellular

responses to stretch, with local production resulting in proliferation and growth.[49] Angiotensin II also increases coronary artery permeability, allowing diffusion of growth factors into the myocardial interstitium.[50] It is known to cause necrosis and fibrosis through its cytotoxic effect on cardiac myocytes.[51] Increased aldosterone production as a result of increased angiotensin II has hemodynamic consequences and stimulates collagen synthesis by myocardial fibroblasts.[52] Increased aldosterone levels may also play a role in myocyte death through their effect on electrolyte balance.[52]

Additional Factors that Influence Remodeling

- The effects on remodeling of factors other than those related specifically to the renin angiotensin system (RAS) and the sympathetic nervous system (SNS) are currently under investigation and include endothelin, cytokines (tumor necrosis factors [TNF] and interleukins) and nitric oxide (NO) production and oxidative stress.
- Endothelins are potent vasoconstrictor peptides, the levels of which are known to be elevated in HF.[53] Endothelin blockade has been shown to be beneficial in animal models and patients with HF.[41,54]
- Cytokines are proteins secreted by cells in response to a variety of stimuli including environmental stress. Circulating levels of the cytokine TNF-alpha are known to be raised in cachectic patients with chronic HF. This elevation has been associated with the marked activation of the RAS seen in patients with end stage disease.[55,56] Data from the Studies of Left Ventricular Dysfunction (SOLVD) indicated that proinflammatory cytokines increase in patients as their functional HF classification deteriorates.[57] Data have also shown that stimulation with pathophysiologic concentrations of TNF-alpha provokes a time-dependent increase in LV remodeling in animal models of HF.[58]
- Oxidative stress is the term used to describe an imbalance between production of oxygen free radicals and antioxidant defenses,[59] the importance of which is increasingly emerging with respect to LV dysfunction and HF progressionreviewed by Ferrari, et al.[59] Cell viability depends on a complex interaction of inducers and suppressors of apoptosis, which are susceptible to modulation by cytokines such as TNF-alpha.[60] Cytokines indirectly increase apoptosis through their effect on the death domain within the cytoplasmic portion of the TNF receptor-1. They also exert a direct cytotoxic effect leading to necrosis. Both apoptosis and necrosis cause further deterioration in the composition and function of the ventricle.[59,,61,62]

The Main Component of Cardiac Remodeling

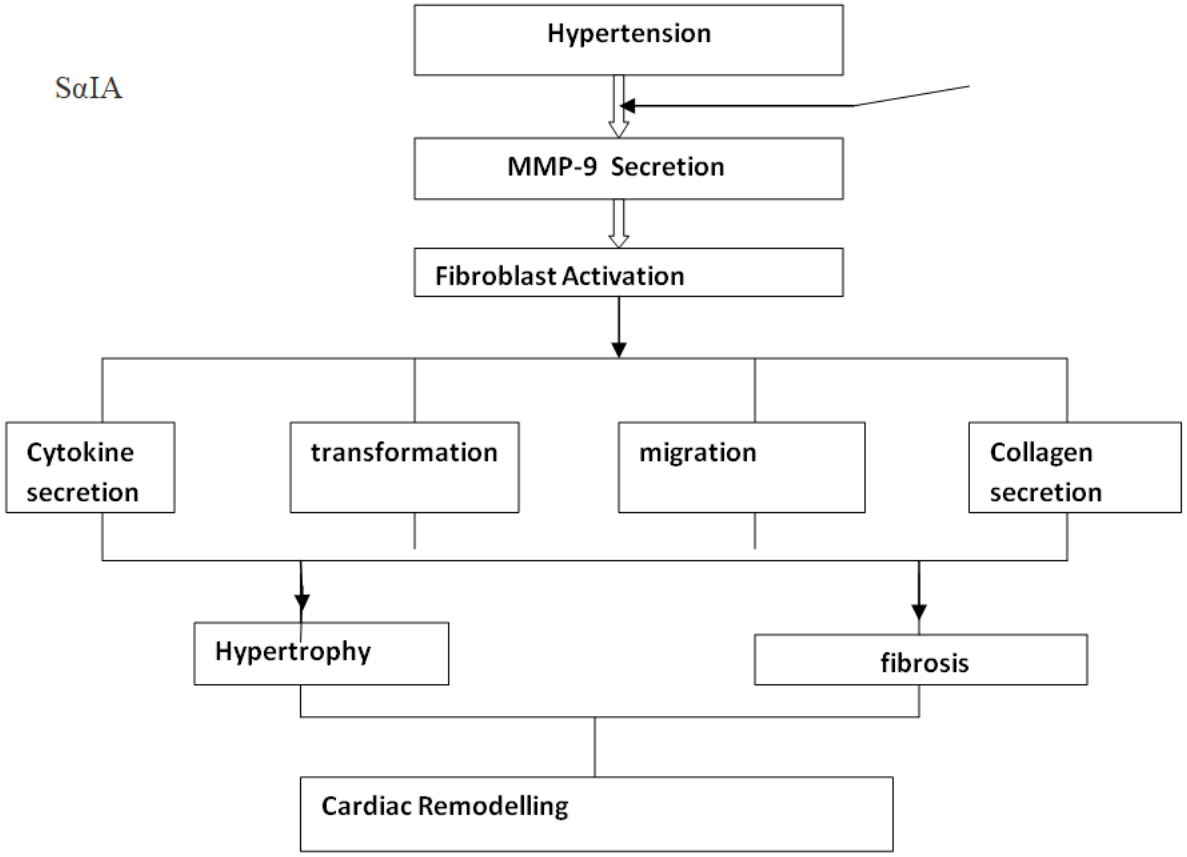
Cardiac Myocytes: Myocytes and other cardiac cell types are believed to be fundamentally involved in the remodeling process. Of all cardiovascular wall components, myocytes have received much attention in view of their contractile activity and numeric contribution to heart mass. As the result of an insult, 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.[63] 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.[64] 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.[65]

The Role of Fibroblast Proliferation: 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 noninfarcted regions of the ventricle, thus contributing to remodeling.[66,67] The relative contribution of the interstitium to the remodeling process is, however, not clear.

The Role of Collagen Degradation: 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.[68,69] 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.[70,71]

The Role of Apoptosis: A working hypothesis for the role of apoptosis in HF is that progressive LV dysfunction occurs, in part, as a result of ongoing myocyte cell death.[72] The importance of this type of cell death in human cardiac remodeling is not yet firmly established, but it has been demonstrated to occur at an increased rate after injury due to ischemia, reperfusion and MI.[73] Apoptosis may be an important regulatory mechanism involved in the adaptive response to pressure overload in which initial apoptosis is linked to cardiac hypertrophy.[74] Other well-known triggers of apoptosis include cytokines (especially TNF-alpha and the interleukins), oxidative stress and mitochondrial damage.[75,76] Recent evidence suggests that myocytes may, in fact, reproduce within the mature heart and may do so at an increased rate in the injured heart.[77] Clearly, if confirmed, such a process must be considered, as well as apoptosis, in the overall remodeling process.

Cardiac Remodeling due to Hypertension



Treatment of Cardiac Remodelling

Many factors influence the time course and extent of remodeling, including the severity of the injury, secondary events (recurrent ischemia or infarction), neurohormonal activation, genetic factors and gene expression, and treatment. Medications may attenuate remodeling; Angiotensin-converting enzyme (ACE) inhibitors have been consistently shown to decrease remodeling in animal models or transmural infarction and chronic pressure overload. Clinical trials have shown that ACE inhibitor therapy after myocardial infarction leads to improved myocardial performance, improved ejection fraction, and decreased mortality compared to patients treated with placebo. Likewise, inhibition of aldosterone, either directly or indirectly, leads to improvement in remodeling.[78] Carvedilol, a 3rd generation beta blocker, may actually reverse the remodeling process by reducing left ventricular volumes and improving systolic function.[79,80] Early correction of congenital heart defects, if appropriate, may prevent remodeling, as will treatment of chronic hypertension or valvular heart disease. Often, reverse remodeling, or improvement in left ventricular function, will also be seen. Diuretics have been used in the treatment of patients with HF since 1919, with the discovery of the diuretic trait of mercury. Currently, loop diuretics, thiazide diuretics, and aldosterone antagonists are commonly used in patients with HF to remove excess volume and relieve symptoms.[81]

CONCLUSION

ACE inhibitors, ARB Blockers, Beta blockers is the most effective to treat cardiac remodeling . Scientist has discovered new medicines for cardiac remodeling are Diuretics, Anti- diabetic drugs, Insulin sensitizers drugs. These drugs are gives faster relief in cardiac remodelling.

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