

Cardiac remodelling: General aspects and mechanisms

Henrique Budib Dorsa Pontes MS¹, Jose Carlos Dorsa Vieira Pontes PhD², Euler de Azevedo Neto MS¹, Alexandre Henrique Zangari MD³, Joao Victor Cunha Miranda MS¹, Otoni Moreira Gomes PhD⁴

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The progression of heart failure is related to cardiac remodelling, which represents the sequence of events at the molecular, cellular and interstitial levels, leading to changes in the size, mass, geometry and function of the heart. Cardiac remodelling involves both adaptive and maladaptive phases of development. At the initial stage, it represents an adaptive response to maintain cardiac output, whereas in the late stage, it results in the occurrence of heart failure. Oxidative stress appears to be the main factor that induces transition of cardiac hypertrophy 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

Heart failure (HF) is a worldwide health problem that affects approximately 26 million individuals (1). It is known that heart disease progresses to HF, and there is a link between cardiac remodelling and the development of HF. Cardiac remodelling is defined as a group of molecular, cellular and interstitial changes that manifest clinically as alterations in the size, mass, geometry and function of the heart after a stressful stimulus (2). This process is triggered by ischemia (myocardial infarction) (3,4), inflammation (myocarditis) (2), hemodynamic overload (workload by volume or pressure) (5) and neurohormonal activation (6,7). 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 (8). As a result of this phenomenon, the heart develops cellular changes such as myocyte hypertrophy (2), necrosis (9), apoptosis (10-12), fibroblast proliferation (13), increased fibrillar collagen (14) and fibrosis (15). At the macroscopic level, it manifests as alterations in geometry of the heart (the chambers turn from an elliptical shape to a spherical shape), which is associated with progressive left ventricular dysfunction (2). Furthermore, this process involves abnormalities in energy metabolism, altered expression or function of contractile proteins, abnormalities in the events related to excitation-contraction coupling and changes in the extracellular matrix (ECM) (16). The present article aims to describe the pathophysiology of cardiac remodelling during the development of HF.

OXIDATIVE STRESS AS A MAJOR EVENT IN CARDIAC REMODELLING

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 (17,18). ROS have four main sources: interaction of leukocytes with cytokines; abnormalities in mitochondrial respiratory chain; increased NAD(P)H

fibrosis and progressive loss of cardiomyocytes. Elements that play a fundamental role at the initial stages of cardiac remodelling and are associated with cardiac hypertrophy include neurohormonal activation, represented by the elevation of angiotensin II and norepinephrine levels. On the other hand, prolonged neurohormonal activation, as well as inflammatory signalling due to increased levels of tumour necrosis factor- α and transforming growth factor- β , may be involved in the late stages of cardiac remodelling associated with heart failure. In its initial stages, cardiac remodelling appears to serve as an adaptive mechanism, whereas in its late stages this process is associated with molecular and cellular defects leading to the development of heart failure.

Key Words: Cardiac remodelling; Cardiac hypertrophy; Heart failure; Neurohormonal activation; Oxidative stress; TNF- α ; TGF- β

oxidase reactivity; and increased xanthine oxidase function (19). During stressful events, the arachidonic acid cycle releases proinflammatory cytokines that interact with chemotactic leukocytes (neutrophils and macrophages) and release ROS in the tissue, leading to oxidative stress (20). It may be noted that oxidative stress has been shown to induce myocardial hypertrophy, cellular dysfunction, ECM remodelling, continuous inflammation and progressive myocyte loss by apoptosis (19).

Under normal conditions, a small amount of ROS are produced in the mitochondrial respiratory chain; this small quantity of O₂⁻ is detoxified by the antioxidant system. However, in HF, mitochondria release O₂⁻ in significant quantities in the presence of NADH (21). Particularly in conditions in which oxygen availability is decreased, mitochondrial production of ROS is enhanced (22). During the development of HF, the levels of different hormones, such as angiotensin II and endothelin-1, are elevated in addition to tumour growth factor- α , which increase NAD(P)H oxidase activity (23-25) and lead to ROS production (26). Xanthine oxidase enzyme expression and function are also elevated in HF, representing an additional source of ROS. Experimental studies have demonstrated the benefits of treatment with allopurinol, a xanthine oxidase inhibitor, in some animal models of HF (27-29).

ROS AND CARDIAC HYPERTROPHY SIGNALLING

'Redox signalling' is the term that defines ROS modulation of the activity of several subcellular pathways that can induce specific regulation in myocyte phenotype (30). 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. Some subcellular pathways have already been described (30-32). Low levels of H₂O₂ 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:

¹UNIDERP, University for the Development of the Pantanal Region; ²UFMS, Federal University of Mato Grosso do Sul, ³Cardiovascular Service;

⁴UFMG, Federal University of Minas Gerais, Cardiomed, Campo Grande, Mato Grosso do Sul, Brazil

Correspondence and reprints: Dr Henrique Budib Dorsa Pontes, University for the Development of the Pantanal Region, Mato Grosso do Sul, Brazil, 79002-121. E-mail henriquedorsa01@gmail.com



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p38 kinases; c-Jun N-terminal kinases; and extracellular regulated kinases (ERK) (31). 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 (33). 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 (34).

There are signal transduction pathways that are associated with the development of pathological fibrosis. The calcium/calmodulin activated protein phosphatase (calcineurin) pathway, which is activated during a sustained period of intracellular calcium elevation, facilitates attachment to the nuclear factor of activated T (NAFT) cells. Mice overexpressing an activated mutant calcineurin showed an increase in heart size, geometrical disorganization and extensive collagen deposition (35). Another kinase pathway involves Ca²⁺/calmodulin-dependent kinase II (CaMKII), reflected by its expression and activity are enhanced in HF (36). Rats overexpressing CaMKII showed chamber dilation, myocyte enlargement and high levels of fibrosis (37). It is noted that an important change in the phenotype of the hypertrophied heart is the transition of the expression of myosin heavy chain (MHC) gene expression. Under physiological conditions, α -MHC, which promotes faster shortening velocity of cardiac myofibres due to high ATPase activity, is predominant (38,42). On the other hand, in HF, there is a downregulation of α -MHC and upregulation of β -MHC, which is expressed in fetal genes, with less ATPase activity (39,40,41,42). It has been shown that there is a correlation between the expression of β -MHC and the degree of cardiac hypertrophy (43). Thus, cardiac remodelling is invariably associated with a switch of myosin isozyms.

OXIDATIVE STRESS AND NEUROHORMONAL ACTIVATION CAUSE CA²⁺ TRANSPORT DYSFUNCTION

The two major structures that modulate the intracellular concentration of Ca²⁺, the sarcolemma (SL) and the sarcoplasmic reticulum (SR), also exhibit alterations in cardiac remodelling (44). In physiological conditions, the excitation-contraction process is activated after a small quantity of Ca²⁺ influx through SL, which in turn stimulates a release of Ca²⁺ from the SR. In the relaxation phase, it is estimated that approximately 80% of the free cytoplasmic Ca²⁺ is accumulated in the SR (45). In cardiac remodelling, modifications in the expression of the sarcolemmal Na⁺Ca²⁺ exchanger (which uses the influx of Na⁺ to remove the intracellular Ca²⁺) and the SR Ca²⁺-ATPase (SERCA) (which is responsible for Ca²⁺ sequestration during diastolic phase) have been reported (46). In this condition, messenger RNA and proteins levels of SERCA are reduced, whereas that of the Na⁺Ca²⁺ exchanger are elevated or unaltered (46,47). Decreased levels of SERCA reduce Ca²⁺ diastolic sequestration, leading to an abnormal force-frequency relationship and a decreased developed tension (48). The elevated expression and function of the Na⁺Ca²⁺ exchanger can lead to a large amount of Na⁺ influx, which is further associated with potential membrane depolarization that can generate amplified arrhythmogenesis (49). The expression of SR phospholamban protein (a SERCA inhibitor and decreases Ca²⁺ sequestration) is depressed, representing an adaptive mechanism to compensate for SERCA dysfunction in HF (50,51).

In cardiac remodelling, both the sympathetic nervous system and the renin-angiotensin system (RAS) are activated, and different studies have demonstrated their relationship with dysfunction of intracellular Ca²⁺ handling (52,53). ROS also modifies the proteins involved in excitation-contraction coupling, and there is evidence that ROS can suppress L-type Ca²⁺ channels, causing oxidative interaction with Ca²⁺ ATPase in the SR to inhibit Ca²⁺ uptake and

enhance the probability of opening ryanodine receptors (54). Accordingly, both oxidative stress and neurohormonal activation can be regarded to play a critical role in the adjustment of Ca²⁺ handling during the development of cardiac remodelling.

CARDIAC INJURY LEADS TO FIBROSIS

Cardiac fibroblasts (CFBs) represent a large cell population, corresponding to approximately two-thirds of the cells in the heart. On the other hand, cardiomyocytes constitute approximately two-thirds of the volume of the myocardial tissue (55). Aside from playing a key role in maintaining cardiac geometry, structure, biochemical processes and function, CFBs are essential for optimal electrical conduction in the myocardium (56,57). CFBs play a fundamental role in ECM homeostasis and remodelling. In normal conditions, ECM is composed of fibrillar collagen types I and III, fibronectin, laminin, fibrillin, elastin, glycoproteins and proteoglycans; CFBs are the primary source of these ECM proteins (58). CFBs also produce matrix metalloproteinases (MMPs) as well as tissue inhibitors of MMPs (TIMPs), which are ECM-regulatory proteins. MMPs are proteases that degrade ECM proteins and TIMPs can inhibit MMP function; their balanced equilibrium is critical for ECM homeostasis (59). Fibrosis is a response of hyperactivity of CFBs that proliferates in response to certain stressful stimuli, and recruitment and proliferation of circulating bone marrow-derived cells that infiltrate the myocardium and transform into CFBs (60). It has been reported in some studies that increased levels of collagen synthesis biomarkers (PICP, PINP, PIIINCP, PIIINP) and reduced serum levels of collagen type I degradation biomarker (CITP), result in collagen deposition and fibrosis in cardiac remodelling (61,62).

Transforming growth factor-beta (TGF- β) plays a critical role in fibroblast phenotype modulation and gene expression, inducing interstitial fibrosis (63). TGF- β suppresses ECM degradation by inhibiting MMP expression and inducing TIMPs synthesis. In addition, TGF- β also induces conversion of different fibroblasts into CFBs, and enhances ECM proteins synthesis (64, 65). Several studies have provided evidence indicating a direct link between the RAS and TGF- β pathway, suggesting TGF- β acts downstream of angiotensin II (66,67,68). ECM remodelling may be the key in cardiac remodelling disease. Impairment of the ECM network structure disorganizes and interrupts myocardial cells and blood vessel connections, leading to a decrease in heart function and destruction of structural integrity. Fibrosis and overproduction of ECM proteins lead to enhanced stiffness of the myocardium wall, systolic and diastolic dysfunction and distorted architecture (60,62).

CONCLUSIONS

Cardiac remodelling is both an adaptive and maladaptive response to various stressful stimuli. After cardiac stress, many changes at the macroscopic and microscopic level occur, leading to the development of cardiomyocyte hypertrophy, intracellular Ca²⁺ overload, fibrosis and apoptosis. The major events that result in cardiac remodelling include the production of ROS, neurohormonal activation of the sympathetic nervous system and RAS, and increase in the levels of inflammatory cytokines such as TGF- β and TNF- α . Despite great progress in this area during more than 40 years of research, cardiac remodelling remains an important topic that warrants more investigation, perhaps because it is the key step in preventing the progress of HF.

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