



Post Myocardial Infarction Remodelling (Review Article)

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Abstract

The biomechanical model of heart failure is the accepted model that can explain the progressive nature of the disease. Left ventricle (LV) remodelling is the main cause of heart failure secondary to myocardial infarction (MI). The three major biomechanical mechanisms of remodelling after MI are; infarct expansion, non-ischemic infarct extension and eccentric hypertrophy of non-infarcted myocardium. We reviewed mechanisms of post MI remodelling, current and potential therapies.

Keywords: *remodelling, post infarction, mechanisms.*

INTRODUCTION

Our understanding of heart failure has been progressed through several models. The first model of heart failure was the cardiorenal model, in which heart failure was initially viewed as a problem of excessive salt and water retention caused by renal hypoperfusion. This model was supported by the improvement of volume overload state by diuretics use. Cardiorenal model was gradually replaced by cardioneural model with the observation that heart failure was largely a problem of excessive peripheral vasoconstriction and reduced cardiac output. This model was supported by the improvement of the failing state by angiotensin converting enzyme (ACE) inhibitors as afterload reducers. Over the past decades, these models have given way to a neurohormonal model, in which heart failure is understood in terms of the Renin-Angiotensin-aldosterone System (RAAS) activation and sympathetic over activity that firstly act as

adoptive cardiovascular responses but then exert maladaptive and deleterious effects on heart and circulation. This model was supported by the improvement of the failing state by RAAS blockade either by ACE inhibitors or Angiotensin II (AII) receptors blockers and the use of β blockers.

While this model has great value in identifying mechanisms and in developing effective therapies, it does not completely explain the progressive nature of the disease. To explain the progressive nature of heart failure, a biomechanical model was proposed ⁽¹⁾ that demonstrate the structural basis of heart failure and postulates that LV remodelling may contribute independently to its progression ⁽²⁾. While the causes of heart failure are widely diverse, myocardial infarction is one of the most common etiological factors. Heart failure secondary to MI largely depends on post MI remodelling. LV remodelling is defined as a

change in the size, geometry and/or composition of the left ventricular myocardium.

The myocardium consists of 3 integrated components: cells, extracellular matrix, and the capillary microcirculation. Nearly 75% of the cells in the healthy heart are nonmyocytes, which include fibroblasts ⁽³⁾ that account for 90% to 95% of nonmyocyte cell ⁽⁴⁾. The cardiomyocyte is terminally differentiated and develops tension by shortening and accounting for about 25% of the cells. The extracellular matrix provides a stress-tolerant, viscoelastic scaffold that couples myocytes and maintains the spatial relations between the myofilaments and their capillary microcirculation ⁽⁵⁾. The collagen framework couples adjacent myocytes by intercellular struts that align myofilaments to optimize force development, distribute force evenly to the ventricular walls, and prevent sarcomeric deformation ⁽⁶⁾. Fibroblasts and myofibroblasts ⁽⁷⁾ produce most of the extracellular matrix macromolecules, including collagen, the principal structural protein ⁽⁸⁾. About 85% of total collagen is type I which form thick fibers that confer tensile strength and resistance to stretch and deformation, whereas ~11% of total collagen is type III which form thin fibers that confer resilience ⁽⁸⁾. The coronary microcirculation can be thought as a system of interconnecting pathways with conduit small arteries, distribution vessels (arterioles), exchanged vessels (capillaries) and reception vessels (venules and veins). The close matching of coronary blood flow to myocardial oxygen consumption has been attributed to metabolic mechanisms. When myocardial oxygen consumption increases, the coronary circulation compensates by increasing myocardial blood flow through dilatation of coronary microvessels.

The normal left ventricle geometry is bullet-shaped with gradual tapering of the diameter toward the apex (Figure 1). This bullet-shaped geometry is noted in the echocardiographic apical four- and two-chambers views ⁽⁹⁾. The sequences of events after myocardial ischemia induced coagulative necrosis run in three phases. The first

inflammatory phase is characterized by the infiltration of neutrophils that begin to clear the infarct of necrotic cardiomyocytes and cellular debris. Collagen breakdown begins within 3 hours of infarction and is induced by serine proteases such as plasmin and the release of matrix metalloproteinases-8 (MMP8) from neutrophils ⁽¹⁰⁾. This is followed 2–3 days later by the second proliferative phase during which monocytes invade the infarct and differentiate into macrophages. During the proliferative phase, neovessels are formed to support the proliferation of myofibroblasts in the infarct. The myofibroblasts elaborate extracellular matrix proteins including the collagen necessary for scar formation ⁽¹¹⁾. During the final phase, fibroblasts undergo apoptosis, neovessels regress from the infarct and the collagen-based matrix matures by condensation into mature scar. It is critical that strong and mature scar to be formed as early as possible since the structurally weakened infarct is subjected to infarct expansion during the proliferative phase ⁽¹²⁾.

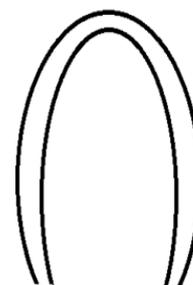


Figure 1: Normal bullet-shaped LV

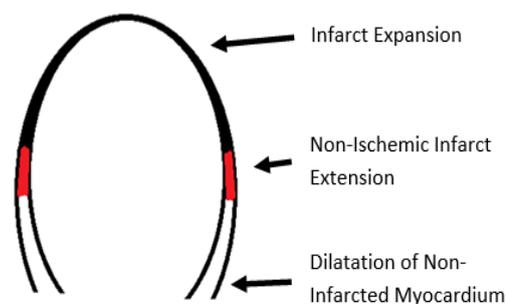


Figure 2: Biomechanical mechanisms contributing to post MI remodelling

The three major biomechanical mechanisms contributing to the increase in LV chamber volume over time after MI are: 1) expansion of the infarct in the sub-acute phase ⁽¹³⁾, 2) subsequent non-ischemic infarct extension into the adjacent noninfarcted region ⁽¹⁴⁾, and 3) hypertrophy and dilatation of non-infarcted myocardium in the chronic phase ⁽¹⁵⁾ (Figure 2).

I-THE INFARCT

The most widely recognized and well-understood biomechanism underlying LV remodelling after MI is infarct expansion. Infarct expansion is referred to the radial thinning and circumferential increase in the extent of a transmural infarct that occurs during days to weeks following acute MI ⁽¹¹⁾. Infarct expansion represents an acute remodelling phenomenon and carries significant prognostic implications. It is more common after anteroapical myocardial infarction than infoposterior infarction ⁽¹⁶⁾. Abnormal geometry is most apparent in the apical four-chambers view and may involve rounding of the apex or asymmetry of apical shape as opposed to smooth bullet-like tapering ⁽¹⁶⁾. Infarct expansion is observed most frequently in large transmural infarctions ⁽¹⁷⁾. The contention that a small, well-healed infarct is not a significant stimulus for LV remodelling is supported by the observation that small infarct scars detected in patients using the cardiac MRI technique of late gadolinium-enhancement are not associated with LV remodelling. Also, the workload placed on the heart and the number of heartbeats occurring prior to scar maturation are critical factors in the progression of infarct expansion ⁽¹¹⁾.

The initial digestion of collagen intercellular struts in the initial inflammatory phase is responsible for the slippage of the necrotic myofilaments that causes infarct expansion ⁽¹⁸⁾. Moreover, high levels of filling pressure in vitro have been shown to injure the connective tissue matrix more than the myocytes ⁽¹⁹⁾. Thus, both the elevation in intracavitary pressure and ischemia may contribute to connective tissue disruption favoring

the spatial rearrangement of myocytes in the wall after infarction. The observation of greater myocyte slippage in the region bordering the infarct than in the remote zone of the ventricle appears to favor this explanation ⁽²⁰⁾. The degradation of connective tissue matrix is mediated mainly by MMPs ⁽²¹⁾. The collagenases (MMP-1, -8, and -13) are highly specific and primarily cleave fibrillar collagens at specific sites, thereby destroying structural integrity. The gelatinases (MMP-2 and -9) degrade the denatured fibrillar collagens, other collagen types, and elastins ⁽²²⁾. Once MMPs bind to collagen fibrils and begin their attack, they could continue to act until all collagen is degraded unless they are inhibited by the Tissue Inhibitors of MMPs (TIMPs), which provide an essential inhibitory mechanism against uncontrolled degradation by MMPs ⁽²²⁾. Transcription from MMP genes to pro-MMPs is stimulated by IL-1, platelet-derived growth factor (PDGF), and TNF α , and inhibited by TGF β . Activation of pro-MMPs to active MMPs is stimulated by the plasminogen activator/plasmin system. Inhibition of activated MMPs by TIMPs and drugs, such as tetracyclines, anthracyclines, synthetic TIMP inhibitors, regulate the proteolysis of connective tissue matrix.

Factors influence the intensity of post myocardial infarction left ventricular remodelling are infarction size, anterior location and transmural extent of the infarction ⁽¹¹⁾. Early reperfusion of totally occluded coronary arteries with thrombolysis and/or percutaneous coronary intervention (PCI) for MI reduces infarct size and LV remodelling after the onset of MI ⁽²³⁾. Furthermore, successful reperfusion greatly affects the reduction in infarct size and improves left ventricular (LV) function ⁽²⁴⁾. Patency of infarct related artery (IRA) supports the healing myocardium with sufficient inflammatory cells, allows rapid clearance of the necrotic myocytes, and fibroblasts which allow rapid formation of a strong scar ⁽²⁵⁾. Impaired healing capacity either by; age related impaired fibroblast function ⁽²⁶⁾, or by the administration of

NSAIDs or corticosteroid leads to weak scar formation and consequent infarction expansion⁽²⁷⁾. Experimental data suggested that smoking, by increasing oxidative stress, may intensify post-MI remodelling⁽²⁸⁾. Likewise, some clinical trials suggested that high baseline glycemia may also predict remodelling⁽²⁹⁾. Admission hyperglycemia intensifies post-MI remodelling regardless of diabetic state⁽³⁰⁾.

Transient episodes of angina preceding MI protect the myocardium from ischemic damage. This phenomenon is known as the preconditioning effect⁽²⁴⁾. In cases of MI, patients with prodromal angina seem to have reduced infarct size and better prognoses⁽³¹⁾. In addition, LV remodelling is prevented after the onset of MI⁽³¹⁾. The cellular pathway of preconditioning is the activation of protein kinase C that is triggered by the adenosine A₁ and A₃ receptors⁽³²⁾. After activation of protein kinase C, mitochondrial and sarcolemmal adenosine triphosphate (ATP)-sensitive K channels play a key role⁽³³⁾. This is associated with a reduction in action potential duration, which is believed to reduce calcium inflow to myocytes⁽³²⁾. The inhibition and reduction of calcium inflow to myocytes may have cardioprotective effects on the ischemic heart, and K-ATP channel openers as adenosine and nicorandil may help this action⁽²³⁾.

On the other hand, the postconditioning effect, short-lived episodes achieved by repetitive occlusion and reperfusion in the early minutes after revascularization of MI, reduces the size of the MI⁽²⁴⁾ and hence post infarction remodelling. The mechanism can be explained, although it is not fully understood, by the activation of reperfusion injury salvage kinase pathway, which refers to a group of protein kinases, and inhibition of mitochondrial permeability transition pore opening⁽³⁴⁾. *Bell and Yellon* showed that atorvastatin administered at the onset of reperfusion attenuated lethal reperfusion injury in mouse hearts by activating the reperfusion injury salvage kinase pathway⁽³⁵⁾. In humans, oral pravastatin before reperfusion with PCI has been

reported to reduce infarction size and to ameliorate LV function in patients with MI⁽³⁶⁾.

Left ventricular wall stress, which is the infarct expansion force, is affected by both arterial blood pressure and LV end-diastolic pressure. In response to increased ventricular stress and loss of contractile elements, the infarct expands and the noninfarcted zone continues to dilate and hypertrophy for months or years⁽²⁶⁾. In these actions, activation of RAAS and increased norepinephrine release greatly affect LV remodelling⁽³⁷⁾. Inhibition of RAAS by various pharmacological agents was approved to reduce LV remodelling⁽²⁴⁾. Only acetyl salicylic acid is approved to be used in acute MI and the use of any NSAIDs is contraindicated to patients with acute MI⁽²⁴⁾.

During healing phase of MI, fibrosis can spill over the remote myocardium, which subsequently have deleterious effect in LV function. Antifibrotic therapy can be used to inhibit or reverse excess cardiac fibrosis and its adverse effects on LV function⁽³⁸⁾. Potential approaches include long-term suppression of TGF β , connective tissue growth factor (CTGF), prolyl-4-hydroxylase (P4H), and MMPs. Potential agents include: Pirfenidone which inhibit TGF β -stimulated collagen synthesis and profibrotic cytokines, Pentoxifilline which inhibit platelet derived growth factor (PDGF) and enhance adenosine, and 4, 5-dimethylthiazolium chloride (ALT-711) which can break excessive cross-links due to advanced glycation end products⁽³⁸⁾. However, antifibrotic therapy is likely to be a two-edged sword since antifibrotic agents exert global actions that can affect both the infarct zone and non-infarct zone. Experimental data on the temporal evolution of healing and connective tissue matrix remodelling⁽³⁸⁾ suggest that these agents could produce adverse connective tissue matrix remodelling in the infarct zone during the highly vulnerable periods of early stages of healing after MI⁽³⁸⁾.

II- THE ADJACENT NONINFARCTED ZONE

The adjacent noninfarcted region is defined by its proximity to the infarct (whether it is necrotic tissue early after MI or mature scar late after MI). The adjacent noninfarcted region is a moving target whose position is defined by the progressive extension of scar tissue into viable myocardium⁽¹¹⁾. While one might suspect that infarct extension is the result of residual ischemia, microsphere-based perfusion studies have shown that it can occur in fully perfused tissue myocardium⁽¹⁴⁾. Cardiomyocytes lying at the border of the scar and adjacent noninfarcted regions experience the greatest stress⁽³⁹⁾. The juxtaposition of adjacent noninfarcted region between non-contractile infarct scar and the contractile myocardium puts it in a great tethering. The tethering imposed on these cardiomyocytes induces oxidative stress and activates pro-inflammatory pathways within these cells. The expression of TNF α ⁽⁴⁰⁾, nitric oxide and oxidative stress mediators⁽⁴¹⁾ have been documented in cardiomyocytes bordering the infarct scar. The combination of oxidative and nitrosative stress ultimately leads to apoptosis of cardiomyocytes adjoining the mature scar, replacement with fibrous tissue and extension of the infarct scar⁽¹¹⁾ with the formation of an apoptotic wave toward the remote myocardium. ACE inhibition and β blockade would be anticipated to reduce the local stresses experienced by cardiomyocytes located in the adjacent noninfarcted region. Anti-inflammatory agents may have some beneficial effect against non-ischemic infarct extension. However, it is desirable to withhold anti-inflammatory therapy which, can interfere with the formation of strong and mature scar. The more selective TNF- α antagonists and anti-caspases may be of a great benefit and are under extensive studies as a potential anti remodelling therapy.

III-THE REMOTE NONINFARCTED ZONE

The remote noninfarcted region can be defined as the non-ischemic myocardium lying beyond the adjacent region. The increased workload imposed by large MI can elicit a hypertrophic response in the remote region⁽¹¹⁾. Within a cylinder, the law of Laplace states that; wall tension is equal to the pressure within the cylinder times the radius of curvature of the wall over wall thickness:

$$(t = pr/h)$$

Where (t) is wall tension (dyn/cm), (p) is pressure (dyn/cm²), (r) is the radius (cm), and (h) is wall thickness. Dilatation of the heart decreases cardiac efficiency, unless hypertrophy is sufficient to normalize wall stress⁽⁴²⁾. Two basic patterns of cardiac hypertrophy occur in response to hemodynamic overload. In pressure overload hypertrophy, the increase in systolic wall stress leads to the addition of sarcomeres in parallel, an increase in myocyte cross-sectional area, and increased LV wall thickening. This pattern of remodelling has been referred to as "concentric" hypertrophy. In contrast, in volume overload hypertrophy, increased diastolic wall stress leads to an increase in myocyte length with the addition of sarcomeres in series, thereby engendering increased LV dilation. This pattern of remodelling has been referred to as "eccentric hypertrophy" (so named because of the position of the heart in the chest), or a "dilated" phenotype⁽⁴³⁾.

As necrotic myocytes slip past each other, the infarct zone thins and elongates, especially in patients with large anterior infarcts, leading to infarct expansion. As the ventricle dilates during the first few hours to days after infarction, regional and global wall stress increase according to Laplace's law⁽⁴⁴⁾. LV remodelling post-MI is primarily a state of volume overload and thus leads primarily to myocyte lengthening and thus eccentric hypertrophy⁽¹¹⁾. The increased wall tension imposed on cardiomyocytes in the remote region after MI lead to the re-induction of a fetal gene expression implicated in hypertrophic response. Calcineurin is a protein phosphatase that dephosphorylates transcription factors of the

nuclear factor of activated T cells (NFAT) family, which leads to their translocation to the nucleus to activate target genes. It is well established that activation of the calcineurin/NFAT pathway is sufficient for the development of cardiac hypertrophy and failure⁽⁴⁵⁾. However, establishing whether calcineurin is necessary for this process has been more problematic. Conflicting results in studies in vivo using the calcineurin inhibitors cyclosporine A (CsA) and FK506 to treat various models of hypertrophy. Many studies have reported attenuation of hypertrophy by CsA and FK506⁽⁴⁶⁾. However, there have also been studies that reported no significant attenuation of hypertrophy in vivo. In humans, immunosuppressive therapy after solid-organ transplantation is associated with cardiac hypertrophy secondary to drug-induced hypertension and⁽⁴⁷⁾ suggesting that; much higher doses of CsA (or FK506) are required to suppress calcineurin activity in the hypertrophic heart relative to T cells suppression⁽⁴⁸⁾.

Small G proteins play an important role in sarcomeric and cytoskeletal organization, hallmark features of the hypertrophic phenotype. Small G proteins also regulate such diverse processes as cell growth, division and survival, membrane trafficking, and cellular motility⁽⁴⁹⁾. Several small GTPases have been implicated in hypertrophy and studied as therapeutic targets. Ras, the first small G protein shown to be involved in cardiac hypertrophy, induces a significant increase in cardiac mass when a constitutively active mutant is overexpressed in transgenic mouse hearts⁽⁵⁰⁾. The Rho family of small G proteins, consisting of RhoA, Rac, and Cdc42 subfamilies⁽⁵¹⁾. RhoA activates several protein kinases, specifically Rho-associated kinase (ROCK), and potentiates GATA4 transcriptional activity to induce a hypertrophic phenotype in neonatal rat cardiomyocytes⁽⁵²⁾. Signal transduction by small G proteins requires isoprenylation, which in turn leads to membrane targeting. Cholesterol-lowering drugs of the statin class (HMG-CoA

reductase inhibitors) block isoprenylation, thereby inhibiting small G protein function. Accordingly, both AII-induced⁽⁵³⁾ and phenylephrine-induced⁽⁵⁴⁾ cardiomyocyte hypertrophy are prevented by statin treatment in vitro. Simvastatin significantly reduces hypertrophy in rats with pressure overload due to aortic banding⁽⁵⁵⁾. Fluvastatin increases survival in a murine model of myocardial infarction⁽⁵⁶⁾. This effect is associated with attenuation of left ventricular dilation and lower end-diastolic pressures, which suggests a favourable effect on post infarction ventricular remodelling. In short, calcineurin inhibitors and statins are potential novel therapies that can inhibit fetal gene expression program and retard the progressive hypertrophic response in the remote myocardium.

Summary

Current therapies for decreasing infarct zone expansion are strategies that limit infarction size and decrease wall stress by using ACE inhibitors and β blockers. Antifibrotic therapy by suppression of TGF β , CTGF, P4H, and MMPs is a two-edged sword that could potentially produce adverse connective tissue matrix remodelling in the infarct zone during the highly vulnerable periods of early stages of healing after MI. ACE inhibition and beta-blockade reduce the local stresses experienced by cardiomyocytes located in the adjacent noninfarcted region. Although, anti-inflammatory therapy can decrease remodelling in the adjacent noninfarcted region, they can interfere with the formation of mature scar and should be withheld. The more selective TNF α antagonists and anti-caspases may be of a great benefits and are under extensive studies. Calcineurin inhibitors and statins are potential therapies that can inhibit fetal gene expression program and retard the progressive hypertrophic response in the remote myocardium and they are under extensive studies.

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