Post Infarct Left Ventricular Remodeling: Current Concept in Pathophysiology and Management

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Introduction:
Ventricular remodeling is the process by which ventricular size, shape and function are regulated by mechanical, neurohormonal and genetic factors.[1] Remodeling may be physiological and adaptive during normal growth or pathological due to acute myocardial infraction (AMI), cardiomyopathy, hypertension or valvular heat disease. This article will re view left ventricular (LV) remodeling after acute myocardial infraction, pathophysiological mechanisms and therapeutic interventions.

Pathophysiology:
Postinfarction left ventricular remodeling:

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 cardiomyocyte is terminally differentiated and develops tension by shortening. The extra cellular matrix provides a stress-tolerant, viscoelastic scaffold consisting of type I and type III collagen that couples myocytes and maintains the spatial relations between the myofilaments and their capillary microcirculation. The collagen framework couples adjacent myocytes by intercellular status that align myofilaments to optimize force development, distribute force evenly to the ventricular walls, and prevent sarcomeric deformation.

Myocardial infraction cause acute inflammation in the infarct zone and hemodynamic abnormality. Acute inflammatory reaction causes the migration of macrophages, monocytes, and neutrophils into the infarct zone; this initiates intracellular signaling and neurohormonal activation. The loss of myocardium due to acute myocardial infarction results in diminished systolic performance and stokes volume. Changes in circulatory hemodynamics and determinate primarily by the degree of myocyte loss, the stimulation of the sympathetic nervous system and renin angiotensin aldosterone system and the release of natriuretic peptides. These factors initiates and subsequently modulates reparative changes, which include dilatation hypertrophy and the formation of a discrete collagen scar. Ventricular remodeling may continue for weeks or months until the distending forces and counterbalanced by the tensile strength of the collagen scar. This balance is determined by the size, locations and transmurality of the infarct, the extent of myocardial stunning, the patency of the infarct-related artery and local tropic factors.[1,2]

Postinfarction remodeling has been arbitrarily divided into an early phase (within 72 hours) and a late phase (beyond 72 hours).

i) Early remodeling

ii) Late remodeling

Early Remodeling:
The early phase involves expansion of the infarct zone,[3] which may result in early ventlicular rupture or aneurysm formation. Infarct expansion results from the degradation of the intermyocyte collagen struts by serine proteases and the activation of matrix metalloproteinases (MMPs) released from neutrophils? Infarct expansion occurs within hours of myocyte injury, results in wall thinning and ventricular dilation and causes the elevation of diastolic and systolic wall stresses. Increased wall stress is a powerful stimulus for hypertrophy mediated by mechanoreceptors and

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transduced to intracellular signaling, party via angiotensin II (Ang II) release, which initiates the increased synthesis of contractile assembly units. Adaptive responses are invoked that preserve stroke volume by involving the noninfracted remote myocardium. Infarct expansion causes the deformation of the border zone and remote myocardium, which alters Frank / Starling relations and augments shorteninf./Perturbations in circulatory hemodynamics trigger the symptathetic adrenergic system, which stimulates catecholamine synthesis bye the adrenal medulla and spillover from sympthatetic nerve terminals, activates the renin-angiotensin-aldosterone system and stimulates the production ofatrial and brain natriuretic peptides (ANP and BNPf Augmented shortening and increased heart

rate from sympthetic stimulation result in hyperkinesis of the noninfarcted myocardium and temporary circulatory compensation. In addition. the natriuretic peptides reduce intravascular volume and systemic vascular resistance, normalize ventricular filling, and imfrove pump function.

Late Remodeling:

Late remodeling involves the left ventricle globally. The failure to normahze increased wall stresses results in progressive dilatation, recruitment of border zone myocardium into the scar, and deterioration in contractile function. Remodeling involves myocyte hypertrophy and alterations in ventricular architecture to distribute the increased wall stresses more evenly as the extra-cellular matrix forms a collagen scar to stabilize the distending forces and prevent further deformation. Myocyte hypertrophy is demonstrable microscopically, with and up to l\Vo increase in cell volume and mural hypertrophy by in series sarcomeric replication, without a change in sarcomere length.

Remodeling and Hypertrophy:

Myocyte hypoertrophy is an adaptive response during postinfarction remodeling that offsets increased load, attenuates progressive dilatation and stabiiizes contractile function. Hypoteension after infarction activates the renin angiotensin system (RAS) aldosterone axis, catecholamine production by adrenal medulla, the spillover from sympathetic nerve terminals and the secretion of natriuretic peptides. Enhanced norepinephrine (NE) release contributes directly and indirectly to the hypertrophic response, Stirnulation of p1 adrenoreceptorc by NE leads to myocyte hypertrophy viaihe Gq-dependent signaling pathway.[7] The activation of p1 adrenoreceptors in the juxtaglomerular apparatus induces renin release, which enhances the production of Ang IL Increased Ang II production, induced by the diminished stretch activation of vascular smooth muscle cells in the juxtaglomerular apparatus, promotes the presynaptic release of NEloand blocks its reuptake, increases catecholamine synthesis, and potentiates the postsynaptic action of NE. In addition, Ang II and NE may augment ET-I release, which is another stimulus for myocyte hypertrophy and stimulates the section of ANP, ANP in turn, inhibits the production of catecholamines, Ang II, ET-I and aldosterone.

These changes enhance local Angiostensin II production, which is the likely stimulus for

hypertrophy in noninfarcted myocardium. In addition to the activation of the RAS and adrenergic receptors locally, small mechanical strains induced by elevated wall stresses sensed by infracted and noninfarceted myocardium have been implicated in hypertrophy.[7]

Mechanical stretch results in the secretion of Angiotensin II from cytoplasmic granules, and this stretch-induced hypertrophic response is mediated by ATI receptors.[8,9]

Finally activation of calcium dysendantyrosin kinase, activation of protein kinase, and mitogen activated (MAP) kinase, and S6 kinase all induce secretion of Angiofusin II incluce hypertrophy of myocytes both at infarcted zone and in non infarcted areas is the maior factor for remodeling of the heart.

Collagen Degradation:

Collagen breakdown begins within 3 hours of infarction and is induced by serine proteases such as plasmin and the release of MMP8 from neutrophils.[4] The initial digestion of collagen intercellular struts is responsible for the slippage of the necrotic myofilaments that causes infarct expansion.[3] PKC has been implicated in the induction of MMP transcription in that Ang II, ET-

1, tumor necrosis factor, and catecholamines, which cause receptor medicated increases in PKC are associated with an increase in MMPs.

Collagenolytic activity is confined to regions of injury by tissue inhibitors of the rnetalloprclteinases (TIMPs). These low-molecular-weight proteins (TIMPs) from high-affinity complexes with activated MMPs and neutralize collagen degradation by blocking the catalytic domain of MMPs.[10] TIMPs are induced in the infarct zone within 6 hours, peak by day 2, and return to normal by 14 days.[4]

Triggers for Tissue Repair:

Myocardial repair is triggered by cytokines released from injured myocytes. The cytokine TGF-â1 increases early in the infarct zone, stimulating macrophage and fibroblast chemotaxis and fibroblast proliferation. An increase in interferon activates macrophages to produce nitric oxide, which increases vascular permeability and confines the cellular inflammatory response to the infarct zone.[11] Activated macrophages are genetically transformed to express ACF which provides a local source of Ang II that is regulated independently of plasma Ang II but plays a pivotal role in reparative fibrosis. The early release of TGF-â1 from necrotic myocytes and macrophages is also important in the phenotypic transformation of interstitial fibroblasts to myofibroblasts, which elaborated receptors to Ang II, TGF-â1, and ET-1.

Synthesis of collagen types 1 and 3 by myofibroblasts is-modulated by several factors, including Ang Il-related mechanical deformation, fibroblast growth factor, platelet-derived growth factor, ANP and bradykinin-mediated prostaglandin E2 and nitric oxide release. By inhibiting fibroblast growth ANP may retard collgen synthesis and limit proliferative remodeling.[12]

Aldosterone is synthesised by myofibroblasts and has concentration in the heart that is >l7-fold greater that that is in plasma.[13] Aldosterone, which is regulated by nitric oxide, ANP and Ang II stimulates the transcription of collagen type I and type III mRNA. This action is blocked by spironolactone which implicates the mineralocorticoid receptor in collagen synthesis.

Deposition of tyep III and type I collagen occurs predominantly in the infarct zone; however, it also occurs in noninfarcted myocardium when intercellular signaling is potentiated by extensive myocyte necrosis. Type III collagen mRNA increases by day 2 and remains elevated for 3 weeks; type I collagen mRNA increases by day 4 and may remain elevated for up to 3 months. Collagen is detectable microscopically by day 7 and then increases dramatically, such that by 28 days, the necrotic myocytes are entirely replaced by fibrous tissue.[4] After the formation of a scar that equilities distending and resiraining forces, collagen formation is down regulated and most myofibrobtasts undergo apoptosis.

Therapeutic Interventions

The effects of therapies designed to prevent or attenuate postinfarction left ventricular remodeling are best considered with reference to the pathophysiological mechanisms involved.

Thrombolysis

Thrombolysis is of proven value in the acute myocardial infarction, in which the primary objectives are limiting infarct size and salvaging ischemic myocardium. Thrombolysis is indicated in all patients of acute transmural myocardial infarction presenting within the therapeutic window and have no contraindication to this type of therapy. Beyond the acute phase, ventricular remodeling is influenced most by infarct artery patency, ventricular loading conditions, neurohormonal activation and local tissue growth factors.[14]

Infarct Artery Patency

Reperfusion may salvage endocardial tissue and restore stunned myocardium in the infarct border zone. Reperfused infarct with contraction-band necrosis may have greater tensile strength and fewer propensities to expansion. However, infarct size, location and collateral flow determine the likelihood of late remodeling.

Several studies have demonstrated a benefit from myocardial reperfusion, with reduced infarct size and associated improvement in regional and global ventricular function.[14] The independent prognostic importance of infarct-related artery patency has emerged from studies in which patience has correlated closely with change in left ventricular volume and function. Use of novel Gp Iib/IIIa platelet inhibitors to preserve the capillary

microcirculation and minimize plugging from the aggregation of platelets, monocytes and macrophages in combination with early restoratin of flow to the infarct zone by primary angioplasty or thrombolysis (open artery hypothesis) might further improve myocyte salvage and limit remodeling.

Pharmacological Interventions

Once infarct evolution has occurred, pharmacological intervention may minimize infarct expansion and ventricular dilatation and improve the long term prognosis.

Nitroglycerine

Intiavenous nitroglycerin limits infarct size, infarct expansion, infarct-related complications and mortality for up to one year.[15] The long-term beneficial effects of transdermal nitroglycerin on left ventricular remodeling after myocardial infarction have also been reported.[16]

ACE Inhibitors

The efficacy of ACE inhibitors in attenuating let ventricular dilatation after myocardial infarction was first demonstrated in the rats and this effect on remodeling was associated with improved survival.

A recent systematic overview of data from five long term randomized trials showed an overall 28% reduction in death, myocardial infraction and hospital admission for heart failure in patients with position fraction left ventricular dysfunction treated with ACE inhibitors.[17,18]

Activation of the renin angiotensin system in the first few days after acute myocardial infarction can increase the heart rate and systemic vascular resistance and decrease coronary artery perfusion, thus leading to infarct expansion. This could account for the early benefits of ACE inhibitors observed in the fourth international studv oflnfarct survival.

The mechanism of ACE inhibitor action is due in part to peripheral vasodilation, neurohumoral effects and the attenuation of ventricular dilatation. There may be additional benefits for the coronary circulation and intrinsic plasminogen activating system. ACE inhibitors may act directly on myocardial tissue pre venting the inappropriate growth and hypertrophy stimulated by angiotensin II. They may also reduce the number of ischemic events, as suggested by data from the studies of left ventricular dysfunction (SOLVD) and survival and ventricular enlargement (SAVE).[17] Patients with postinfarction left ventricular dysfunction or heart failure should be treated with ACE

inhibitors without delay. Alternatively all patients should be treated with ACE inhibitors initially and therapy continued depending on subsequent assessment of left ventricular function.

Angiotensing Receptor Blockers

ELITE II study[19] demonstrated that losartan, an angiotensin receptor blocker, shows a survival benefit to the same degree as captopril, an angiotensing converting enzyme inhibitor, does in patients with heart failure. However, recent OPTIMAAL study showed that clinical outcomes after Iosartan are not superior to those after captopril in patients with AMI.

β-Blockade

The effects of p-blockade on positnfarction left ventricular remodeling have been little studied. Preliminary data suggest that carvedilil may attenuate remodeling, an effect associated with a significant reduction in subsequent adverse cardiac events.[21] The effects of ACE inhibition and p-blockade seem complementary. After myocardial infarction and in chronic heart failure, ACE inhibition impOroves remodeling and primary reduces deaths from progressive heart failure. In chronic heart failure caused by ischemia, p-blockade with carvedilol can reverse remodeling, which may progress despite standard treatment, including ACE inhibition.[22] The mortality benefit from p-blockade in chronic heart faiiure, which is now clearly established, is due to a reduction in both progressive heart failure and sudden death. Thus, in patients with significant left vernacular dysfunction or heart failure after myocardial infarction, combination neurohormonal blockade may be optimal, although occasionally limited by hypotension.

The mechanism behind the ability of â-Blockade to decrease mortality in chronic heart failure is thought .to involve the combination of an antiarrhythmic effect and improved hemodynamic function of the left ventricle, itself caused by a shower heart rate and inhibition of the detrimental

neurohumoral activation virtually always present in chronic heart failure.

It has been suggested that â-Blockade benefits patients with a wide range of resting baseline heart rates, and not only those with evidence of sympathetic hyperactivation. It has also been suggested that long term â-Blockade in heart failure improves left ventricular contractility and mechanical work without increasing myocardial oxygen consumption. Other mechanisms include improved diastolic function, direct protection of myocytes against excess catecholamines and improved regional wall motion. B-Blockers may also have a favorable effect on hibernating myocardium caused by imbalance between myocardial oxygen supply and demand.

Carvedilol, metoprolol and bisoprolol added to standard therapy including an ACE inhibitor have reduced mortality and morbidity in large-scale studies of ischemic and nonischemic heart failure. Metoprolol and bisoprolol are selective â1-adrenoceptor blockers. Carvedilol is a nonselective, $â_1$-adrenegic receptor antagonist that also blocks $á_1$-adrenoceptors, providing more comprehensive neurohumoral antagonism. It is also a potent antioxidant and thus may prevent the loss of cardiac myocytes that occurs in heart failure as a result of oxidative stress.[21,22]

In patients on long-term treatment after acute myocardial infarction complicated by left ventricular systolic dysfunction, carvedilol reduced the frequencies of all cause and cardiovascular mortality and recurrent nonfatal myocardial infarctions. The reduction in all cause mortality was additional to the effects of ACE inhibitors and re-perfusion therapy.

Thus, the effects of ACE inhibition and â-Blockade appear complementary and both decrease mortality from progressive heart failure. ACE inhibition also controls remodeling while â-Blockade improves myocardial performance and lowers the risk of sudden death. Ln summary, in significant left ventricular dysfunction or heart failure after myocardial infraction, combined neurohumoral blockade may be optimal, although occasionally limited by hypotension.

Synchronized Biventricular Pacinng:

Cardiac resynchronization therapy (CRT) employs atrial sensed synchronous biventricular pacing with optimization of the atrioventricular delay to trigger ventricular contraction immediately following atrial systole. It prolongs left ventricular filling time, and particularly restore interventricular and intraventricular activation and contraction towards normal. One-third of patients with clinical systolic heart failure have prolonged intraventricular conduction as evidence by increased electrocardiographic QRS duration. Prolonged intraventricular conduction causes major changes in the cardiac periods within the cardiac cycle and it associated with decreased survival.[23]

Importantly, CRT did not simply attenuate progressive LV dilatation such as that which occurs with ACE inhibitor or ARB therapy, but resulted in decreased ventricular volumes below baseline values, consistent with reverse remodeling.[24]

Future Clinical Research and Management:

Ventricular remodeling can be considered a primary target for treatment and a reliable surrogate for long term outcomes. The future challenge must be the primary prevention of myocardial infarction in patients at a high risk for coronary disease. In addition, new therapeutic strategies should be targeted to limit remodeling by the controlled modulation of the molecular and cellular factors involved in tissue repair, including hypertrophy, fibrosis and the capillary microcirculation.

Cardiac remodeling may be defined as expression of the genome in molecular, cellular and interstitial changes that are manifested clinically as changes in the size, shape and function of the heart after cardiac injury. The process is influenced by hemodynamic load, neurohumoral activation and other factors still under investigation.

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