Left Ventricular Remodeling After Myocardial Infarction
Pathophysiology and Therapy

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Left ventricular remodeling is the process by which ventricular size, shape, and function are regulated by mechanical, neurohormonal, and genetic factors.[1,2] Remodeling may be physiological and adaptive during normal growth or pathological due to myocardial infarction, cardiomyopathy, hypertension, or valvular heart disease (Figure 1). This article will review postinfarction remodeling, pathophysiological mechanisms, and therapeutic intervention.

Pathophysiology

Postinfarction Left Ventricular Remodeling

The acute loss of myocardium results in an abrupt increase in loading conditions that induces a unique pattern of remodeling involving the infarcted border zone and remote noninfarcted myocardium. Myocyte necrosis and the resultant increase in load trigger a cascade of biochemical intracellular signaling processes that 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 are counterbalanced by the tensile strength of the collagen scar. This balance is determined by the size, location, and transmurality of the infarct, the extent of myocardial stunning, the patency of the infarct-related artery, and local tropic factors.[1,3]

The myocardium consists of 3 integrated components: myocytes, extracellular matrix, and the capillary microcirculation that services the contractile unit assembly. Consideration of all 3 components provides important insights into the remodeling process and a rationale for future therapeutic strategies. The cardiomyocyte is terminally differentiated and develops tension by shortening. The extracellular 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.[4,5] 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.[5]

Myocardial infarction results in the migration of macrophages, monocytes, and neutrophils into the infarct zone; this initiates intracellular signaling and neurohormonal activation, which localizes the inflammatory response. Changes in circulatory hemodynamics are determined primarily by the magnitude of myocyte loss, the stimulation of the sympathetic nervous system and renin-angiotensin-aldosterone system, and the release of natriuretic peptides.

Postinfarction remodeling has been arbitrarily divided into an early phase (within 72 hours) and a late phase (beyond 72 hours). The early phase involves expansion of the infarct zone,[5] which may result in early ventricular rupture or aneurysm formation. Late remodeling involves the left ventricle globally and is associated with time-dependent dilatation, the distortion of ventricular shape, and mural hypertrophy. The failure to normalize increased wall stresses results in progressive dilatation, recruitment of border zone myocardium into the scar, and deterioration in contractile function.[1,6]

Early Remodeling

Infarct expansion results from the degradation of the intermyocyte collagen struts by serine proteases and the activation of matrix metalloproteinases (MMPs) released from neutrophils.[7] Infarct expansion occurs within hours of myocyte injury,[3] results in wall thinning and ventricular dilatation, and causes the elevation of diastolic and systolic wall stresses. Early ventricular dilatation due to infarct expansion has been unequivocally demonstrated in man. Increased wall stress is a powerful stimulus for hypertrophy mediated by mechanoreceptors and transduced to intracellular signaling, partly via angiotensin II (Ang II) release, which initiates the increased synthesis of contractile assembly units.[8] Wall stress is also a major determinant of ventricular performance.

Adaptive responses are invoked that preserve stroke volume by involving the noninfarcted remote myocardium.[9] Infarct expansion causes the deformation of the border zone and remote myocardium, which alters Frank/Starling relations and augments shortening.[9] Perturbations in circulatory hemodynamics trigger the sympathetic adrenergic system, which stimulates catecholamine synthesis by the adrenals and spillover from sympathetic nerve terminals, activates the

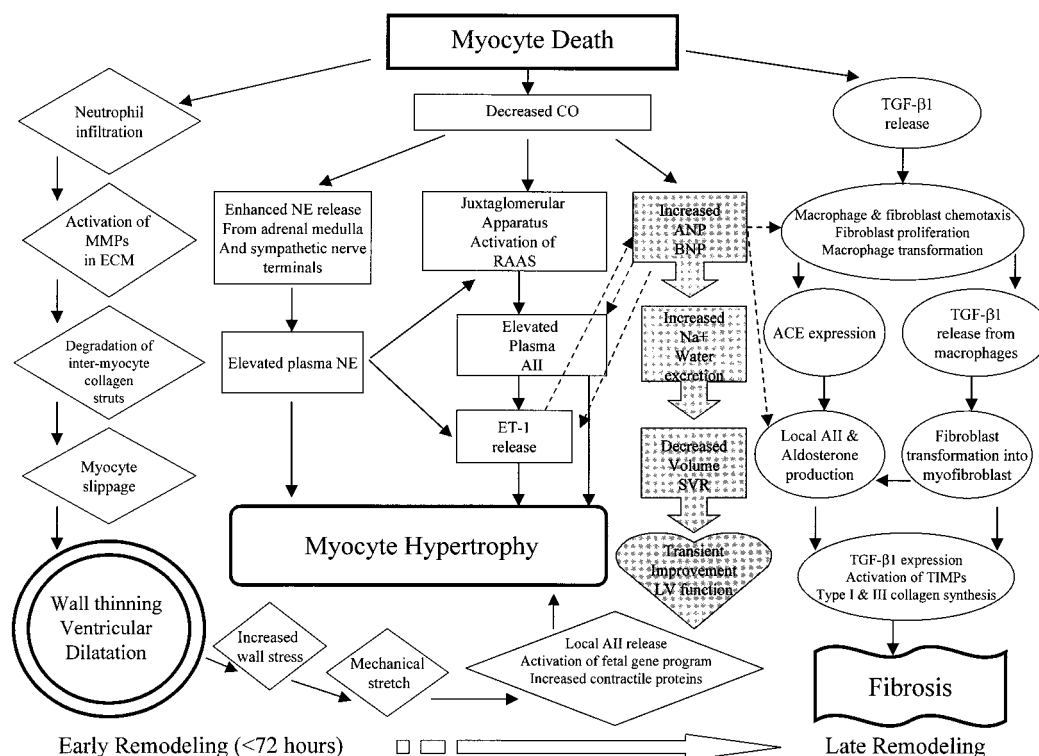*Circulation* is available at http://www.circulationaha.org

Figure 1. Diagrammatic representation of the many factors involved in the pathophysiology of ventricular remodeling. ECM indicates extracellular matrix; RAAS, renin-angiotensin-aldosterone system; CO, cardiac output; SVR, systemic vascular resistance; LV, left ventricular; and AII, angiotensin II.

renin-angiotensin-aldosterone system, and stimulates the production of atrial and brain natriuretic peptides (ANP and BNP).[10] Augmented shortening and increased heart rate from sympathetic 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 improve pump function.

Late Remodeling
Remodeling involves myocyte hypertrophy and alterations in ventricular architecture to distribute the increased wall stresses more evenly as the extracellular matrix forms a collagen scar to stabilize the distending forces and prevent further deformation. Myocyte hypertrophy is demonstrable microscopically, with an up to 70% increase in cell volume[11] and mural hypertrophy by in-series sarcomeric replication, without a change in sarcomere length.

Remodeling and Hypertrophy
Hypertrophy is an adaptive response during postinfarction remodeling that offsets increased load, attenuates progressive dilatation, and stabilizes contractile function.[1] Genes for transcriptional factors, such as c-fos, c-jun, c-myc, Egr-1, natriuretic peptides (ANP, BNP), sarcomeric proteins (β-myosin heavy chain [βMyHC] in rodents, smooth muscle and skeletal α-actins, and myosin light chains 1a and 2a), enzymes (angiotensin-converting enzyme [ACE], βARK), and growth factors (endothelin-1 [ET-1], insulin-like growth factor-1, transforming growth factor [TGF]-β1), are induced and regulated by hypertrophic stimuli.[12–14]

Myocyte hypertrophy is initiated by neurohormonal activation, myocardial stretch, the activation of the local tissue renin-angiotensin system (RAS), and paracrine/autocrine factors. Hypotension after infarction activates the 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. Stimulation of α1 adrenoreceptors by NE leads to myocyte hypertrophy via the Gαq-dependent signaling pathway.[15] The activation of β1 adrenoreceptors in the juxtaglomerular apparatus induces renin release, which enhances the production of Ang II. Increased Ang II production, induced by the diminished stretch activation of vascular smooth muscle cells in the juxtaglomerular apparatus, promotes the presynaptic release of NE and blocks its reuptake, increases catecholamine synthesis, and potentiates the postsynaptic action of NE.[16] In addition, Ang II and NE may augment ET-1 release, which is another stimulus for myocyte hypertrophy and stimulates the secretion of ANP. ANP, in turn, inhibits the production of catecholamines, Ang II, ET-1, and aldosterone.[17]

Serine proteases activate the local RAS in the noninfarcted myocardium, leading to the up-regulation of angiotensinogen gene expression and increased local ACE activity. These changes enhance local Ang II production, which is the likely stimulus for hypertrophy in noninfarcted myocardium.[18] In addition to the activation of the RAS and adrenergic receptors locally, small mechanical strains induced by elevated wall stresses sensed by infarcted and noninfarcted myocardium

have been implicated in hypertrophy.[12] Small mechanical stretches of myocytes demonstrate a tight bidirectional relationship between wall stress and myocyte hypertrophy,[8] which resembles that between stress and hypertrophy in the intact heart. Stretch-induced hypertrophy in cardiomyocytes mimics hemodynamic load–induced hypertrophy, occurs in the absence of neurohormonal stimulation, and does not require active tension development.[12] These noninjurious strains are of similar magnitude to the increased wall stress from ventricular dilatation after infarction.[8]

Mechanical stretch results in the secretion of Ang II from cytoplasmic granules, and this stretch-induced hypertrophic response is mediated by AT1 receptors.[12–14] Through the activation of this G-protein–coupled receptor, multiple signaling pathways are potentially activated. These include the calcium-dependent activation of tyrosine kinase and the activation of protein kinase C (PKC) via inositide signaling (phospholipase Cβ), mitogen-activated protein (MAP) kinase, and S6 kinase.[15] PKC further induces the secretion of Ang II and, by autocrine/paracrine action, secreted Ang II amplifies the signals evoked by mechanical stress. Mechanical stretch from increased wall stress may induce rapid, transient activation of immediate early genes (ie, jun, fos, myc, and Egr-1), followed by the activation of fetal gene program (ie, α-actin, β-MyHC, and ANP) and a time-dependent increase in protein synthesis.[8,12] The role of immediate early genes in hypertrophy is not clear; however, in vitro studies have shown that Egr-1 may be involved in the transcriptional regulation of the α-MyHC gene.[19]

Cardiac hypertrophy is stimulated by a variety of biochemical and physical stimuli and transduced through a common mechanism involving the activation of protein kinase cascades. The receptors for NE, ET-1, and Ang II are similar and are coupled to Gq proteins.[15] The activation of Gqα stimulates phospholipase Cβ, which in turn leads to the production of 1, 2 diacylglycerol and the activation of PKC.[15] Growth factors, including fibroblast growth factor, epidermal growth factor, platelet-derived growth factor, insulin, and insulin-like growth factor, activate receptor tyrosine kinase, p21 ras, and MAP kinase (extracellular regulated kinase or Jun N-terminal kinase). The activation of MAP kinase is a prerequisite for the transcriptional and morphological changes of myocyte hypertrophy.[20] Ang II may also activate p21 ras through the activation of the nonreceptor tyrosine kinase of the src family.[21] Intracellular calcium seems critical for the activation of protein kinases in cardiomyocytes by Ang II and other hypertrophic stimuli before the fetal gene program can be switched on to increase protein synthesis.

Collagen Degradation

The triple-helical structure of collagen renders it resistant to proteolytic degradation, except by MMPs, which are secreted into the extracellular matrix in their latent proenzyme form.[22] The activation of MMPs requires the proteolytic cleavage of a propeptide sequence. MMP1 (collagenase) cleaves collagen into ¾ and ¼ fragments, which are unfolded and degraded by MMP2, MMP9 (gelatinases), and MMP3 (stromelysin).[22] The regulation of the MMPs occurs at 3 levels: transcription, activation, and inhibition.[22]

The temporal sequence of collagen degradation by the MMPs is species-specific.[7,23] Collagen breakdown begins within 3 hours of infarction and is induced by serine proteases such as plasmin and the release of MMP8 from neutrophils.[7] The initial digestion of collagen intercellular struts is responsible for the slippage of the necrotic myofilaments that causes infarct expansion.[5,24] In the rat heart, MMP1 activity is not detectable until day 2 postinfarction, and it peaks at day 7.[7] Activation of MMP1 augments MMP2 activity, which peaks at day 7, whereas MMP9 activity is only detectable by day 4.[7] MMP3 activity is a regulatory step in the activation of the family of MMPs. PKC has been implicated in the induction of MMP transcription in that Ang II, ET-1, tumor necrosis factor-α, and catecholamines, which cause receptor-mediated increases in PKC, are associated with an increase in MMPs.[25]

Collagenolytic activity is confined to regions of injury by tissue inhibitors of the metalloproteinases (TIMPs). These low-molecular-weight proteins (TIMPs) form high-affinity complexes with activated MMPs and neutralize collagen degradation by blocking the catalytic domain of MMPs.[22] TIMPs are induced in the infarct zone within 6 hours, peak by day 2, and return to normal by 14 days.[7] The synthesis of TIMPs is modulated by the levels of activated MMPs, such that collagen degradation reflects the dysequilibrium between MMPs and TIMPs.

Triggers for Tissue Repair

Myocardial repair is triggered by cytokines released from injured myocytes. The cytokine TGF-β1 increases early in the infarct zone, stimulating macrophage and fibroblast chemotaxis and fibroblast proliferation.[26] An increase in γ-interferon activates macrophages to produce nitric oxide, which increases vascular permeability and confines the cellular inflammatory response to the infarct zone.[27] Activated macrophages are genetically transformed to express ACE, which provides a local source of Ang II that is regulated independently of plasma Ang II but plays a pivotal role in reparative fibrosis.[26] The early release of TGF-β1 from necrotic myocytes and macrophages is also important in the phenotypic transformation of interstitial fibroblasts to myofibroblasts, which elaborate receptors to Ang II, TGF-β1, and ET-1.[26,28] Myofibroblasts express genes encoding for procollagen types 1 and 3, generate Ang I and II and receptors for Ang II and TGF-β1 and ET-1; this enables the autoregulation of collagen turnover.[4,26] Synthesis of collagen types 1 and 3 by myofibroblasts is modulated by several factors, including Ang II–related mechanical deformation, fibroblast growth factor, platelet-derived growth factor, ANP, and bradykinin-mediated prostaglandin E2 and nitric oxide release.[4] By inhibiting fibroblast growth, ANP may retard collagen synthesis and limit proliferative remodeling.[17] Mechanical strains also determine the degree of collagen cross-linking and the strength of the mature scar.[29]

Tissue repair is initiated by the formation of a fibrin-fibronectin matrix, which precedes collagen synthesis,[30] to which myofibroblasts become adherent. A complex costimulatory relationship exists between aldosterone, ANP, endothelin, bradykinin, and TGF-β1 in the regulation of collagen synthesis. Aldosterone is synthesised by myofibroblasts and

has a concentration in the heart that is >17-fold greater than that in plasma.[31] 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. The aldosterone-mineralocorticoid receptor complex activates the Ang1 receptor gene to increase the number of Ang1 receptors. Reciprocal stimulation of aldosterone and Ang II amplifies the proliferative and fibrogenic responses of Ang II to up-regulate type I and type III collagen mRNAs, both of which are prevented by Ang1 receptor blockade.[32,33]

Deposition of type 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.[7] 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.[7] After the formation of a scar that equilibrates distending and restraining forces, collagen formation is down-regulated and most myofibroblasts undergo apoptosis.

Therapeutic Intervention

The effects of therapies designed to prevent or attenuate postinfarction left ventricular remodeling are best considered with reference to the pathophysiological mechanisms involved. Thrombolysis limits infarct size, transmurality, and infarct expansion and is of proven benefit in eligible patients. Beyond the acute phase, ventricular remodeling is influenced most by infarct artery patency, ventricular loading conditions, neurohormonal activation, and local tissue growth factors.

Infarct Artery Patency

Although infarct size is a major determinant of ventricular remodeling, late patency of the infarct-related artery or collateral flow to the infarct may confer survival benefit. In a study of patients who did not receive thrombolysis, the degree of perfusion of the infarct-related artery was a more important predictor of left ventricular volume change from 48 hours to 1 month after infarction than infarct size.[34] Reperfusion may salvage endocardial tissue and restore stunned myocardium in the infarct border zone. Reperfused infarcts with contraction-band necrosis may have greater tensile strength and less propensity to expansion. However, infarct size, location, and collateral flow determine the likelihood of late remodeling. A large autopsy series confirmed the association of infarct expansion with large transmural infarcts.[35] Infarct expansion occurred more frequently in the left anterior descending coronary artery than in the right coronary artery, and increased heart weight correlated inversely with expansion. Differences in regional wall thickness, the radius of curvature, and intramural tension also influence infarct expansion and remodeling.

Several studies have demonstrated a benefit from myocardial reperfusion, with reduced infarct size and associated improvement in later regional and global ventricular func-

tion.[36,37] The independent prognostic importance of infarct-related artery patency has emerged from studies in which patency has correlated closely with changes in left ventricular volume and function.[38] The Total Occlusion Study of Canada trial[39] recently demonstrated the benefit of primary stenting compared with angioplasty alone in improving late patency, restenoses, and the need for revascularization in a large group of patients with nonacute coronary occlusions. However, the benefit of the acute percutaneous revascularization of occluded infarct-related arteries on remodeling is unknown.

Pharmacological Intervention

Thrombolysis is of proven value in the acute infarction, in which the primary objectives are limiting infarct size and salvaging ischemic myocardium. Once infarct evolution has occurred, pharmacological intervention may minimize infarct expansion and ventricular dilatation and improve the long-term prognosis.

Nitroglycerin

Intravenous nitroglycerin limits infarct size, infarct expansion, infarct-related complications, and mortality for up to 1 year.[40] The long-term beneficial effects of transdermal nitroglycerin on left ventricular remodeling after myocardial infarction have also been reported.[41] Despite these positive results, the large GISSI-3 trial (Gruppo Italiano per lo Studio della Sopravvivenza nell'infarto Miocardico)[42] and the Fourth International Study of Infarct Survival (ISIS 4)[43] failed to show a significant mortality benefit in patients treated with nitrates after acute myocardial infarction. This may have been due to a null bias related to extensive use of nonstudy nitrates and also to the limited efficacy of the nitrate regimens used. However, there may be a true lack of efficacy of routine nitrate therapy when used concurrently with thrombolysis, aspirin, ACE inhibitors, and β-blockers. Although routine intravenous nitroglycerin may be used during the first 24 hours after myocardial infarction, nitrates are not recommended routinely beyond this time except for specific indications, which include persistent ischemia, hypertension, or heart failure.

ACE Inhibition

The efficacy of ACE inhibitors in attenuating left ventricular dilatation after infarction was first demonstrated in the rat, and this effect on remodeling was associated with improved survival. The effects of captopril, furosemide, and placebo were studied in patients with asymptomatic left ventricular dysfunction (ejection fraction <45%) 1 week after a Q-wave myocardial infarction[44] (Figure 2). Captopril treatment resulted in a significant reduction in left ventricular end-systolic volume index, with increases in stroke volume index and ejection fraction, whereas treatment with furosemide and placebo was associated with significant increases in echocardiographic left ventricular volumes at 1 year. Another study[45] randomized patients with an ejection fraction <45% and without heart failure to receive captopril or placebo at a mean of 18 days after a first anterior myocardial infarction. End-diastolic volume increased in the placebo group at 1 year but not in the captopril group, although the difference between groups was not significant. Although left ventricular dysfunc-
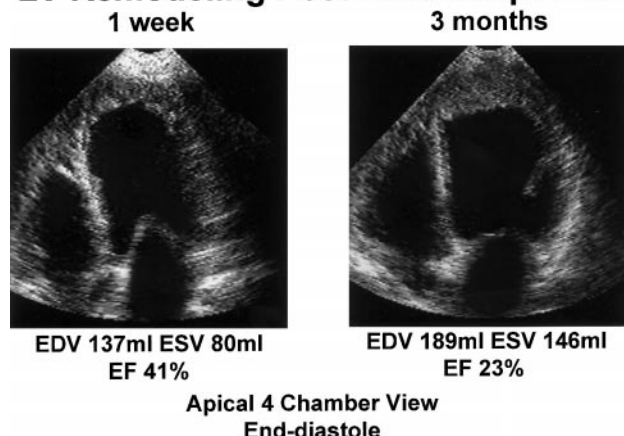
LV Remodeling Post Anteroseptal MI

Figure 2. Left ventricular (LV) remodeling after transmural anteroseptal myocardial infarction (MI): 2D echocardiographic evaluation at 1 week and 3 months. Extensive anteroapical akinesis, progressive dilatation, and dysfunction with increased sphericity are evident, as is the development of apical thrombus. EDV indicates end-diastolic volume; ESV, end-systolic volume; and EF, ejection fraction.

tion can be improved with ACE inhibition commenced 1 week after infarction, earlier intervention seems to provide greater benefit[46] (Figure 3).

The mechanism of improvement with ACE inhibition is related in part to peripheral vasodilatation, ventricular unloading, and the attenuation of ventricular dilatation. There may be additional beneficial effects on the coronary circulation[47] and intrinsic plasminogen-activating system. Although coronary hemodynamic data have suggested a balanced effect of ACE inhibitors on the coronary circulation, one study in patients with heart failure and angina indicated that such treatment may worsen ischemia, because of the hypotension that compromises myocardial perfusion.[48] Importantly, ACE inhibition may have a direct effect on myocardial tissue,[4,8,18] preventing the inappropriate growth and hypertrophy stimulated by Ang II and other growth factors.
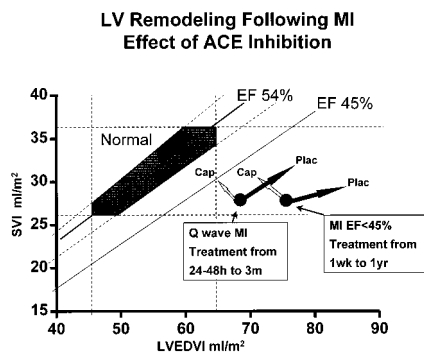

Figure 3. Left ventricular (LV) function plot derived from quantitative 2D echocardiographic data from 2 intervention studies[44,46] using ACE inhibition after myocardial infarction (MI). Postinfarction left ventricular dilatation is greater at 1 week than at 24 to 48 hours after Q-wave infarction. Intervention with captopril (cap, light arrows) prevents or reverses progressive remodeling compared with placebo (plac, dark arrows), with a greater benefit after earlier intervention (from 24 to 48 hours) than after 1 week. SVI indicates stroke volume index, LVEDVI, left ventricular end-diastolic volume index; and EF, ejection fraction.

A number of large studies have demonstrated a survival benefit when ACE inhibitors have been used in all patients with myocardial infarction[42,43] and selectively in patients with left ventricular dysfunction or heart failure.[49,50] The consistent survival benefit of ACE inhibitors compared with other vasodilators and a comparison of short- and long-term effects implicates biological tissue effects in addition to vasodilatation.

Evaluation of ACE inhibitor treatment with captopril given 2 hours after the commencement of streptokinase therapy showed the most benefit on regional wall motion in patients with anterior infarction with reduced infarct-related artery flow.[51] This finding is concordant with the retrospective analysis of the Survival and Ventricular Enlargement study,[52] which showed a reduction in a composite end point in captopril-treated patients with occluded arteries but no such effect in those with patent arteries.

It is recommended that patients with left ventricular dysfunction or heart failure be treated with ACE inhibitors without delay after infarction. Alternatively, all patients should be treated with ACE inhibitors initially, with a review of the need for continuation later on the basis of left ventricular function assessment.

β-Blockade

The effects of β-blockade on postinfarction left ventricular remodeling have been little studied. Preliminary data suggest that carvedilol may attenuate remodeling, an effect associated with a significant reduction in subsequent adverse cardiac events.[53] Whether β-blocking agents provide a benefit additional to ACE inhibitor treatment in patients with left ventricular dysfunction or heart failure after acute myocardial infarction remains unknown. Although the rationale for combination treatment is strong when extrapolating from clinical trials with β-blockers after myocardial infarction generally and after heart failure, definitive data are lacking.

The effects of ACE inhibition and β-blockade seem complementary. After myocardial infarction and in chronic heart failure, ACE inhibition improves remodeling and primarily reduces deaths from progressive heart failure. In chronic heart failure caused by ischemia, β-blockade with carvedilol can reverse remodeling, which may progress despite standard treatment, including ACE inhibition.[54] The mortality benefit from β-blockade in chronic heart failure, which is now clearly established, is due to a reduction in both progressive heart failure and sudden death. Thus, in patients with significant left ventricular dysfunction or heart failure after myocardial infarction, combination neurohormonal blockade may be optimal, although occasionally limited by hypotension.

Future Clinical Research and Management

Ventricular remodeling can be considered a primary target for treatment and a reliable surrogate for long-term outcomes. Noninvasive imaging has provided insights into the mechanisms by which biochemical and cellular changes are translated into alterations in ventricular architecture and function during remodeling. Clinical outcome analyses and reliable, objective, noninvasive measurements of ventricular structure and function currently provide a template for assessing new
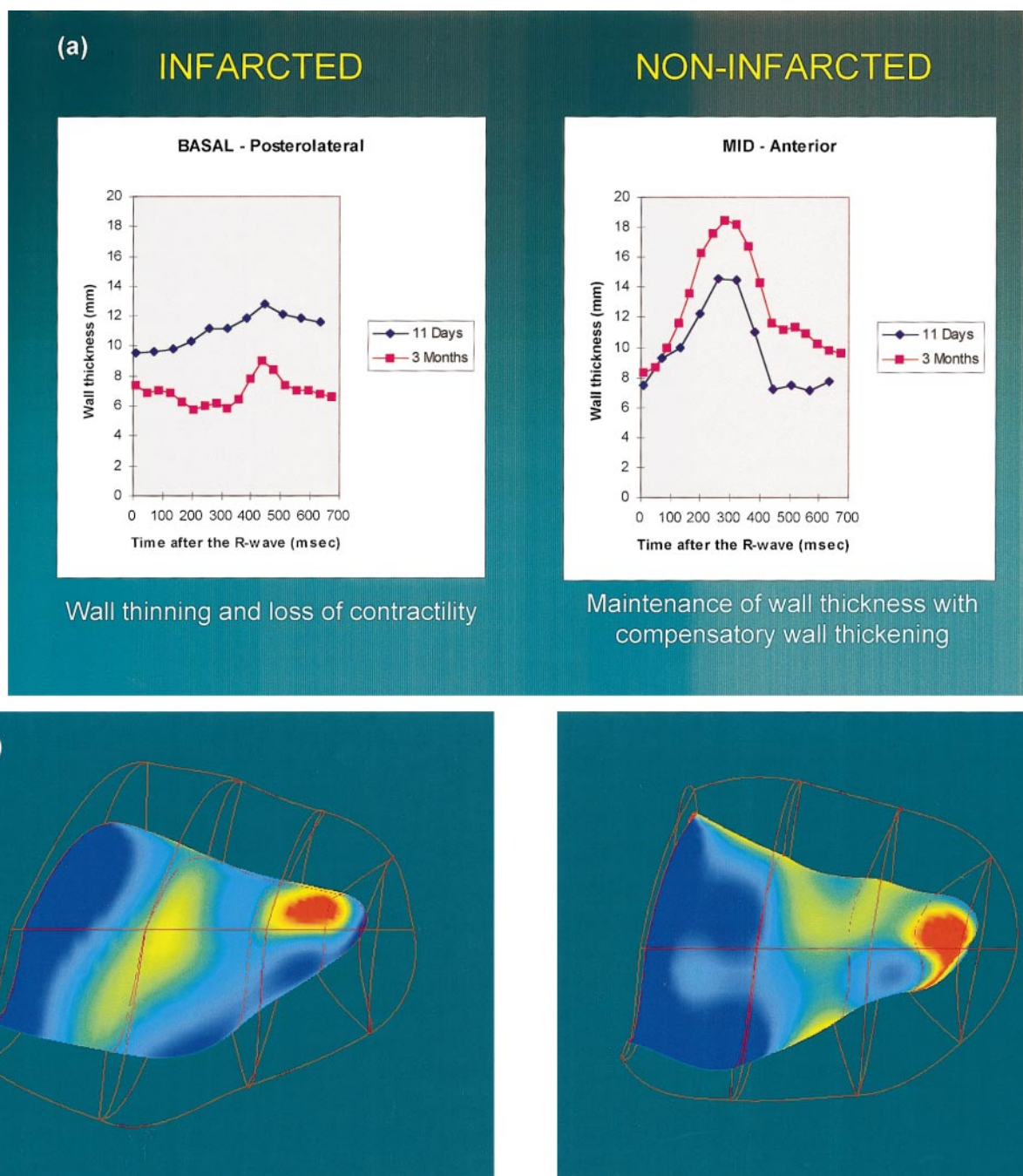
Figure 4. Cardiac MRI of left ventricular remodeling after inferoposterior myocardial infarction: regional wall motion analysis. a, The infarcted basal segment shows akinesis and thinning from 11 days to 3 months compared with the compensatory increase in contraction and thickening anteriorly. b, Three-dimensional shaded endocardial surfaces in lateral projection with a color scale representing wall thickening and showing changes from 11 days to 3 months. Dark blue equates with ≤20% wall thickening; yellow ≥50%, and red ≥80%. Reproduced with permission from Reference 55.

therapies. Cardiac MRI offers even greater accuracy, reductions in sample size requirements for intervention studies, and reliable assessment of individual cases[55] (Figure 4).

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.

Use of novel IIb/IIIa platelet inhibitors to preserve the capillary microcirculation and minimize plugging from the aggregation of platelets, monocytes, and macrophages, in combination with early restoration of flow to the infarct zone by primary angioplasty or thrombolysis (open artery hypothesis), might further improve myocyte salvage and limit remodeling.

Preventing the breakdown of the extracellular collagen scaffold with exogenous MMP inhibitors or increased activity of TIMPs could stiffen the infarct zone, arrest infarct expan-

sion, and prevent ventricular dilatation and the increased wall stress that initiates the intracellular signaling for enzymatic degradation of collagen.

Pharmacological blockade of TGF-β1, which plays a critical role in the development of fibrosis (Figure 1), may potentially reduce or even prevent fibrosis in the infarct and the noninfarct zones, thereby improving ventricular compliance.

The development of new agents that allow modulation of the hypertrophic response triggered by plasma and local neurohormones would include partial blockers of natriuretic peptides, endothelin, and aldosterone receptors that would be similar to current ACE and Ang II receptor-blocking agents or blockers at the second messenger level.

Gene therapy enabling adenoviral gene transfection with vascular endothelial growth factor can enhance intracellular calcium handling and improve the contractile function of cardiomyocytes by the over-expression of sarcoplasmic reticulum Ca^{2+} ATPase in vitro, suggesting that selective gene transfer into hypertrophied myocardium might normalize intracellular calcium handling and provide a means to promote the controlled regression of hypertrophy. Further novel genetic engineering may permit phenotypic transformation of embryonic stem cells into cardiomyocytes or facilitate cardiomyocyte regeneration and engraftment in regions of fibrosis and thinning to restore wall thickness and myocardial mass. Similarly, genetic approaches to modify vascular growth may well be amenable to clinical application in the future.

A more highly integrated, systematic, and focused research approach and increased clinician awareness of the importance of remodeling and opportunities for intervention should ensure more effective management and improved outcomes for patients.

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