

Left Ventricular Remodeling after Myocardial Infarction: Past, Present, and Future

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Abstract

Medical advances in the care of cardiac patients have resulted in more patients surviving an acute myocardial infarction (MI) than ever before. Each year hundreds of thousands of these survivors undergo remodeling of their left ventricle and often progress to clinical congestive heart failure. The extent of remodeling has been linked to the size of the infarct, whether or not the myocardium has been revascularized, and the control of loading conditions. The extent of infarction can be measured several ways, including the amount of enzyme released as well as infarct imaging with nuclear perfusion or magnetic resonance imaging. Methods to prevent adverse remodeling of the ventricle have included pharmacotherapy with beta-blockers, nitrates, and modulators of the renin-angiotensin-aldosterone system. Surgical intervention has proven useful for select patients with aneurysmal areas of remodeling. Researchers are now investigating several approaches to preventing and reversing cardiac remodeling. These include the use of stem cells to regenerate myocardium and post-infarct pacing to prevent remodeling. Improved therapies are needed to help reduce the number of patients progressing from myocardial infarction to end-stage heart failure.

Key Words: Heart failure, left ventricle, remodeling, myocardial infarction.

Introduction

IT IS ESTIMATED THAT 1.2 million Americans had a myocardial infarction and 500,000 died in 2005 (1). Approximately 7.8 million people in the United States have survived an MI. Their hearts undergo adaptive responses to the change in hemodynamics as less myocardium attempts to maintain the same cardiac output as before. The remodeling that occurs begins immediately and may continue for a lifetime (2). While this adaptive remodeling seems beneficial in the short term, over time it becomes deleterious, leading eventually to congestive heart failure.

The cost of treating acute MIs is enormous: it was \$140 billion in 2002 (direct and indirect costs combined) (3). When the costs of congestive heart failure are added to the equation (direct cost of \$22 billion), the consequences of remodeling are better appreciated. Fortunately, there are therapies to reduce post-MI remodeling.

Pathophysiology

The responses to myocardial infarction are numerous, involving many changes at the cellular and molecular levels. Myocardial cell death requires adjustments to account for the increase in workload of the remaining myocardium. The remodeling that occurs includes dilatation, hypertrophy, scar formation, neurohormonal responses, cytokine activation, and oxidative stress (4–6). The extent of remodeling is proportional to the mass of infarcted myocardium, the patency of the infarct-related artery, and ventricular loading conditions (7).

The responses that occur after an MI can be divided into early and late remodeling, with the former occurring in the first 3 days after the MI and the latter occurring more than 3 days after the MI. Early remodeling occurs mainly in the infarct and peri-infarct zones. Late remodeling includes

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changes in the geometry and size of the entire left ventricle.

One of the early changes in ventricular remodeling is infarct expansion, a phenomenon in which the size of the infarct typically increases in the first few days. It does not involve an increase in myocardial necrosis. Instead, the mechanism is postulated to involve cell rupture, reduced intercellular space, stretching of myocytes, and slippage of myocytes, resulting in fewer cells per wall thickness (8). The degree of infarct expansion ranges from the clinically inapparent to ventricular rupture. Factors such as the location of the infarct, size of the initial infarct, thickness of the infarcted myocardium, and loading conditions on the ventricle, contribute to the likelihood and significance of infarct expansion. Up to one-half of anterior wall MIs show infarct expansion, and there is a clear relationship between infarct expansion and a poorer prognosis (9).

Remodeling in the left ventricle (LV) also includes changes to the healthy myocardium. In response to the change in loading conditions, the entire ventricle dilates (10, 11). The process begins immediately and can last for months after the MI. Mitchell et al. studied 52 patients at 3 weeks and then at 1 year after an anterior wall MI, with biplane ventriculography. The contractile segments of the left ventricle elongated and the LV became more spherical in geometry (12, 13). Specifically, after an anterior MI, the LV apex is the most vulnerable region to undergo remodeling: it is the thinnest area and it increases in radius the most (14). This principle was well illustrated by a subgroup of the HEART (Healing and Early Afterload Reducing Trial) trial, in which patients underwent echocardiographic analysis of wall stress. After an anterior MI, the degree of initial apical wall stress correlated to the degree of LV remodeling that occurred at 90 days (15).

Neurohormonal mechanisms compound the alterations in hemodynamics and the remodeling that occurs. The sympathetic nervous system, via norepinephrine-mediated activation of reactive oxygen species and tumor necrosis factor (TNF), has been implicated in inducing apoptosis in cardiomyocytes (16). The further loss of cardiomyocytes contributes to progressive LV dilatation. Another major system that has enhanced activity after an MI is the renin-angiotensin-aldosterone system (RAAS). The body responds to the diminished cardiac output just as it would to blood loss or dehydration. Renin levels are markedly increased, angiotensin II is activated, aldosterone is released, and vasopressin is increased. All of these effects serve to increase plasma volume, decrease

sodium excretion, and increase vascular tone. Within the region of the myocardial infarct, aldosterone increases the deposition of collagen. These two systems—the RAAS and the sympathetic nervous system—play an important role in the changes that occur after an MI. The Figure illustrates the complex interplay between these and other systems that occurs during remodeling.

Infarct Imaging

While a comprehensive review of infarct imaging is beyond the scope of this article, a brief mention is warranted. Determining the location and extent of the infarct provides important prognostic information for the management and therapy of the patient. The most common modalities are echocardiogram, radionuclide angiography, and single photon emission computed tomography (SPECT) imaging. While all of these modalities have been used in clinical trials with good reproducibility, in clinical practice they are less precise. The introduction of cardiac magnetic resonance (CMR) has brought a technology capable of increased sensitivity, increased reproducibility, and better resolution.

In a study of 91 patients with known or suspected coronary artery disease, SPECT and CMR were compared to determine sensitivity and specificity of infarct detection. For subendocardial infarcts SPECT was inferior to CMR imaging (SPECT missed 13%), but it was as good as CMR for transmural infarcts (17). Another area where CMR can have prognostic significance is in evaluating microvascular reperfusion. Abnormalities in microvascular perfusion can occur despite patent coronary arteries. Contrast enhanced CMR with first pass perfusion can demonstrate regions of microvascular obstruction, which correlates with decreased wall motion and increased clinical events (18, 19).

The advantages of CMR can be important clinically; however, the practical application is somewhat limited. Due to the expense, time, and expertise needed to provide and read CMR, only a limited number of centers would be able to perform the studies. For large numbers of patients, echocardiography will still be more available and cost-effective despite any shortcomings.

Pharmacotherapy

Nitrates

Nitroglycerin was first discovered to have pharmaceutical properties in 1847 by Ascanio Sobrero. Since then the fortunes and careers of several men, including Alfred Nobel, Ferid Murad,

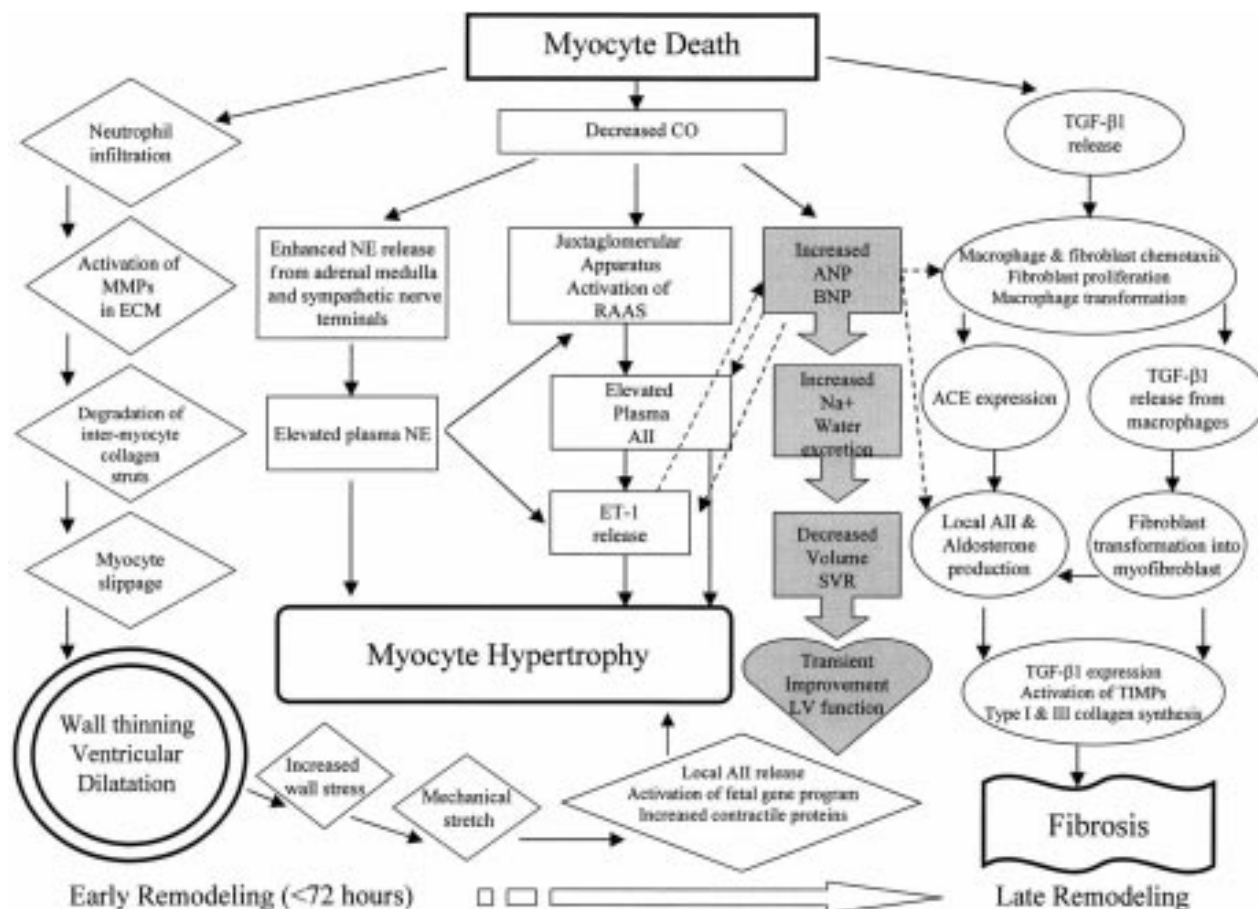


Figure. Proposed mechanism of cardiac remodeling, demonstrating the many factors involved in the pathophysiology of ventricular remodeling. ECM = extracellular matrix; RAAS = renin-angiotensin-aldosterone system; CO = cardiac output; SVR = systemic vascular resistance; LV = left ventricular; AII = angiotensin II; NE = enhanced norepinephrine; TGF = transforming growth factor; ET = endothelin; ANP = atrial natriuretic peptide; BNP = brain natriuretic peptide; TIMP = tissue inhibitor of metalloproteinase.

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Robert Furchgott, Salvador Moncada, and Louis Ignarro (among others), have been closely tied to it. Nitrate-based therapies for acute myocardial infarction have been widely used for several decades. Nitrates have several pharmacologic effects: dilatation of the venous system, which results in decreased preload on the left ventricle; mild arterial dilatation, which results in decreased afterload; and selective dilatation of coronary arteries, which can result in increased myocardial perfusion to the peri-infarct zones. These hemodynamic effects are said to be responsible for limiting infarct size, reducing infarct expansion, and improving ventricular geometry in post-MI patients (20–22). At the molecular level, nitroglycerin effects these hemodynamic changes by its ability to produce nitric oxide, which activates soluble guanylyl cyclase, which in turn produces cyclic guanosine monophosphate (cGMP) and results in decreased intracellular Ca^{++} and vasorelaxation of smooth muscles (23–25). The clinical ben-

efits of increased perfusion include a decrease in ischemic injury and a decrease in infarct size. The beneficial effects are more potent when there is no evidence of clinical hypotension (26). In one trial, the addition of a vasoconstrictor abolished the positive effects of intravenous nitrate therapy, demonstrating that it is mainly the hemodynamic effect of nitrate therapy that is clinically relevant (27).

A meta-analysis done in the pre-thrombolytic era showed a small mortality benefit to nitrate therapy in acute MI, although two large randomized trials in the mid-1990s (GISSI-3 and ISIS-4) did not show a statistically significant benefit (28–30). However, there was significant crossover use of nitrates in the control arms of both studies, which may have exaggerated the benefit of placebo. Despite the shortcomings, there was a very statistically significant ($p < 0.001$) decrease in early mortality (Day 0–1) in the nitrate-treated arm of ISIS-4, but this effect dissipated with

chronic therapy (30). The most current recommendations of the American Heart Association (AHA) for the treatment of acute myocardial infarction, published in 2004, give a class I indication for the use of nitroglycerin by patients with ischemic discomfort, hypertension, or pulmonary congestion (31). While nitroglycerin is still an important therapeutic agent, it has been relegated to a secondary role compared to angiotensin-converting enzyme inhibitors (ACE-I) and beta-blockers.

Angiotensin-Converting Enzyme Inhibitors and Angiotensin Receptor Blockers

ACE-I's work by blocking the conversion of angiotensin I to angiotensin II, which is a potent vasoconstrictor. ACE-I's also block the degradation of bradykinin, which is a mild vasodilator. Angiotensin II has effects that can be deleterious, including sodium and water reabsorption, systemic arteriolar constriction, endothelial dysfunction, increased sympathetic tone, and left ventricular hypertrophy (32–35). A number of angiotensin II receptors have been identified. Most of the hemodynamic effects attributed to angiotensin II are related to its binding to the angiotensin 1 (AT1) receptor.

After a myocardial infarct, levels of the ACE enzyme in the cardiac tissue of rats are elevated (36). Animal studies in the 1980s with the ACE inhibitor captopril showed its potential benefits: in preventing hypertrophy, diminishing already established hypertrophy, and preventing LV dysfunction (37, 38). ACE inhibitors have been found to modulate the increased fibrosis that is seen with activation of angiotensin II, resulting in a more functional myocardium (39). They also improve the hemodynamics after an MI by effecting decreases in afterload and preload. They decrease left ventricular filling pressures by inducing venodilation and enhancing myocardial relaxation. ACE inhibitors dilate the arterial system and thus lower afterload, in part by the resulting accumulation of bradykinin. Many of the hemodynamic effects of ACE inhibitors have been duplicated in similar studies using angiotensin receptor blockers (ARBs). These drugs offer a more selective blockade of angiotensin II, resulting in fewer side effects, such as the cough mediated by bradykinin.

In addition to improvement in indices of LV remodeling such as LV size, volume, and function, several large clinical trials have showed mortality benefit to using ACE inhibitors after acute MI (40, 41). In the Survival and Ventricular Enlargement (SAVE) study, Pfeffer et al. enrolled 2,231 patients with subclinical LV dysfunction (LVEF < 0.40) between 3 and 16 days after an MI and divided them

into a captopril arm and a placebo arm. After 42 months of follow-up, the patients with captopril had a 19% reduction in death (20% vs. 25%), a 25% reduction in recurrent MI, and a 37% reduction in risk of severe congestive heart failure (CHF) (42). Similar results were obtained with the ACE inhibitor trandolapril (TRACE study), with a relative reduction in death at 3 years of 18% (35% vs. 42%) and a strong reduction in progression to severe CHF as well (43). The findings of these early trials have been mostly confirmed by later trials and several meta-analyses have confirmed the mortality and CHF benefits of ACE inhibitors (44–46). Despite the overwhelming evidence supporting their use, clinicians should use judgment on when to initiate therapy. In CONSENSUS II, enalapril was given intravenously on the first day after MI to over 3,000 patients. At 30 days and 180 days, there was a trend towards higher mortality in the enalapril group (7.2% vs. 6.3% and 11.0% vs. 10.2%). The lack of efficacy may be explained by a 12% rate of hypotension in the enalapril group (3% in the placebo arm) (47).

Angiotensin receptor blockers are a newer class of drug than ACE inhibitors and still require more pre-clinical and clinical data to support their use for LV remodeling after MI. Nonetheless, the appeal of a selective drug to block one culprit receptor is undeniable (48–51), especially when some studies have indicated that ACE inhibition is sometimes not complete and diminishes over time. In addition, alternate pathways of angiotensin II generation have been described (52–54). Some studies have also suggested that activation of other AT receptors (e.g., AT2) may actually have beneficial effects opposing cardiac remodeling (55). Unfortunately, clinical trials with ARBs have a disadvantage in comparison to the older ACE inhibitor trials, since patients are much more aggressively treated now after an MI. Thrombolysis, coronary intervention, beta-blockers, ACE inhibitors, statins, and anti-platelets agents are more frequently used than in the past. To date, there are two large multicenter trials that have evaluated ARBs in post-MI patients. Neither one has been overwhelming.

The OPTIMAAL trial, which investigated the effects of losartan and captopril on mortality and morbidity in high-risk patients after acute MI, randomized 5,477 patients with ST-segment elevation MI (STEMI), re-infarction, or heart failure during the acute phase to a target dose of either losartan 50 mg once daily or captopril 50 mg three times a day. All-cause mortality was non-significantly in favor of captopril (16% vs. 18%; $p=0.07$) (56). The negative results of OPTIMAAL were surprising in light of the theoretical benefits of ARBs, and clin-

icians were left to conclude that ACE inhibitors were preferable to ARBs for post-MI patients, but that ARBs could probably be used by those intolerant of ACE inhibitors. One criticism of OPTIMAAL was that the dose of losartan may not have been high enough.

VALIANT (valsartan, captopril, or both in MI complicated by heart failure, LV dysfunction, or both) was completed by Pfeffer et al. soon after OPTIMAAL; it enrolled over 14,000 patients to one of three arms: valsartan 160 mg twice a day, captopril 50 mg three times a day, or valsartan 80 mg twice a day with captopril 50 mg three times a day. The population was moderate-to-high risk with either clinical heart failure or reduced ejection fraction (EF) after an acute MI. After 24 months of follow-up, there was no statistical or meaningful difference in mortality in the three arms (19.5 vs. 19.9 vs. 19.3%) (57). Unlike OPTIMAAL, non-inferiority was proven. Once again it was disappointing that the combined effects of ACE inhibition and AT1 blockade did not translate into improved clinical outcomes. These results were also confirmed anatomically by the VALIANT-Echo study. A 610-patient subgroup of the VALIANT population was enrolled to have baseline and follow-up echocardiograms. Just as there was no difference in hard endpoints, there was also no difference in LV volumes, infarct segment length, or EF on at 20 months between the three groups (58).

Much data has accumulated thus far, providing the benefit of ACE inhibitors in post-MI remodeling and mortality. In light of OPTIMAAL and VALIANT, the data for ARBs is much weaker. Certainly, a patient who does not tolerate ACE inhibitors can use an ARB with some level of comfort, but the ARB should probably not be used as primary therapy. It is also now reasonable to use both if needed for blood pressure control, but such use may be limited by the side effects from combined therapy.

Aldosterone Antagonists

Aldosterone serves an important role in volume homeostasis by preventing the loss of sodium and water when it is activated. It also serves a role in inflammation and repair by activating macrophages, inducing cytokines, stimulating fibroblasts, and increasing the synthesis of type I and III collagens in scar tissue (59–61). It is activated by, and works in coordination with angiotensin II. The simplest description of the RAAS system is that angiotensinogen is cleaved by renin to angiotensin I, which is then converted by ACE

to angiotensin II, which in addition to its own vasoconstrictor properties, causes the activation of aldosterone. This would mean that the ACE inhibitors should abolish the effects of both angiotensin II and aldosterone. Unfortunately, it appears that the initial strong inhibition of aldosterone by ACE inhibitors diminishes with chronic therapy (62, 63). This would make the inhibition of aldosterone a desirable target to inhibit cardiac remodeling (64–67).

Inhibiting aldosterone directly in addition to ACE inhibitor therapy was first evaluated in a study of patients with New York Heart Association (NYHA) Class III and IV chronic heart failure. The RALES trial enrolled 1663 patients to usual care plus 25 mg a day of spironolactone. The trial was ended early after 2 years of follow-up due to a very strong 30% reduction in mortality for patients who were enrolled to spironolactone (35% vs. 46%) (68). In a 261-patient substudy of RALES, serum markers of cardiac fibrosis were measured at baseline and at 6 months. Treatment with spironolactone resulted in reduced mortality only for those patients with elevated levels of procollagen type III amino terminal peptide, a marker of collagen deposition (69). Studies on LV remodeling also demonstrated smaller LV volumes and improved EF for patients administered spironolactone (70).

Although RALES evaluated a population of chronic heart failure patients, and spironolactone had a high incidence of side effects including gynecomastia and sexual dysfunction, the trial gave credence to the benefits of early aldosterone blockade (as seen in animal studies) (71). The EPHESUS trial was designed to determine the effect of eplerenone on post-MI patients. Eplerenone is a selective inhibitor of the mineralocorticoid receptor; its selective action results in fewer side effects. More than 6,600 patients with acute MI, ejection fraction less than 0.4, and heart failure were randomized to optimal medical therapy with eplerenone or placebo (72). After 16 months, there was a 15% relative risk mortality reduction in the eplerenone group (14.4% vs. 16.7%). Significantly, side effects were also dramatically reduced. The effect was impressive, considering that both groups were very well treated with more than 86% on ACE inhibitors, 75% on beta-blockers, 60% on diuretics, 88% on aspirin, and even 47% on statins. Although there was only one trial, the strength of the evidence led the American College of Cardiology and the AHA to give eplerenone a Class I recommendation in its 2004 guidelines for acute myocardial infarction (31).

The RAAS system is a very heavily studied system in the pathophysiology of post-MI left ven-

tricular remodeling. Three separate classes of drugs supported by clinical evidence of their ability to improve remodeling and mortality are now available to antagonize the system. The clinician must now learn how to safely use ACE inhibitors, ARBs, and aldosterone antagonists in post-MI patients without causing undue renal dysfunction, hyperkalemia, or side effects.

Beta-Blockers

Beta-blockers have been proven to be beneficial after acute MI for over 20 years and are strongly recommended by the AHA (73). Their benefits include decreased oxygen demand, decreased afterload, increased coronary perfusion, decreased automaticity, and reduction in the risk of sudden death (74–76). Their early trials occurred before ACE inhibitors were in common use and demonstrated the potent effect of beta-blockers on a relatively low-risk population. Initially, it was believed that beta-blockers would probably be harmful in patients with congestive heart failure (CHF), due to the negative inotropic effects.

In the mid-to-late 1990s, studies found that carvedilol and metoprolol improved the morbidity and mortality of CHF patients (77–80). The putative mechanism involved neurohormonal blockade of excessive sympathetic tone. After the benefits of beta-blockers for CHF patients became apparent, studies were completed showing a similar benefit for patients who had a reduced systolic function in the setting of acute MI (81, 82). While the benefits of beta-blockers were clear, it was uncertain what additional advantage they had when added to an ACE inhibitor and other optimal therapy.

To answer this question, the Effect of Carvedilol on Outcome after Myocardial Infarction in Patients with Left-Ventricular Dysfunction (CAPRICORN) trial was completed, demonstrating the effects of carvedilol on mortality after a myocardial infarction in a high-risk population with a left ventricular EF of < 40%. The trial enrolled 1,959 patients, who were initiated on 6.25 mg twice daily and titrated up to 25 mg twice daily. Although sicker than patients in earlier trials, this was also a much better treated group of patients. Over 97% were using an ACE inhibitor and almost half had received either thrombolysis or angioplasty. The study still managed to show a 3% absolute reduction in mortality at 2 years (12% vs. 15%) (83).

While CAPRICORN looked at the hard endpoints of carvedilol therapy, the CAPRICORN Echo Substudy evaluated echocardiographic parameters of ventricular remodeling in 127 of the pa-

tients. Baseline echocardiograms were done before enrollment, at 1 month, 3 months, and 6 months. The group that received carvedilol had significant improvements in EF and decreased left ventricular end systolic volume, demonstrating that carvedilol could inhibit ventricular remodeling even in addition to background ACE inhibitor therapy (84).

It is of course important to use clinical judgment to determine the timing and dosage of beta-blocker administration. The recently published COMMIT (Clopidogrel and Metoprolol in Myocardial Infarction Trial) enrolled over 45,000 patients with acute MI into an aggressive beta-blocker regimen or to placebo in addition to usual therapy. The risk of reinfarction and ventricular fibrillation was reduced by 10 per 1,000 treated; however, 11 per 1,000 developed clinical shock (85). Similar to CONSENSUS II, this trial illustrates the dangers of protocol-driven medicine and highlights the need for clinical judgment.

The clinical and echocardiographic improvements in left ventricular remodeling after acute myocardial infarction have been well illustrated in the literature. However, the biochemical mechanisms by which beta-blockers reduce LV remodeling is not clear. Li et al. used a rat model of acute MI treated with carvedilol to evaluate the mechanism of action. Cardiac hemodynamics and measurements of inflammatory markers were done to evaluate the biochemical effect of carvedilol on the mechanisms of LV remodeling. Carvedilol decreased the mRNA and protein expression of pro-inflammatory cytokines, including TNF-alpha, interleukin (IL)-1B, and IL-6 (86).

Altered calcium metabolism also plays a role in post-MI remodeling (87–89). In post-MI rats, there is downregulation of sarcoplasmic reticulum Ca⁺⁺ adenophosphatase (SERCA) and upregulation of phospholamban (an inhibitor of SERCA), resulting in decreased local pools of the calcium that is needed for proper excitation-contraction coupling. The alterations in SERCA and phospholamban are reduced by both metoprolol and carvedilol, which results in less dilatation and hypertrophy (90).

Statins

The pleiotropic effects of hydroxymethyl glutaryl (HMG) coenzyme reductase inhibitors, or statins, are now fairly well established (91). They appear to have nonlipid mechanisms that alter endothelial function, coronary plaque stability, thrombus formation, and inflammatory responses. The reductions in the inflammatory marker C-reactive protein (CRP) have been well publicized in

the literature (92–95). In addition to their coronary benefits, the anti-inflammatory and anti-oxidant effects of statins act to inhibit LV remodeling after MI. Simvastatin has been shown to decrease the levels of many inflammatory cytokines including TNF- α , IL-1 β , and IL-6. This is associated with improved echocardiographic parameters of LV remodeling (96). Similarly, atorvastatin was able to inhibit stimulated cardiac fibroblasts from synthesizing collagen (97). The evidence for these benefits is based mostly on *in vitro* and animal studies, but the results are still intriguing.

Rats with surgically induced anterior wall MIs were treated with cerivastatin for 12 weeks. At the end of the study period, the cerivastatin-treated rats had a smaller LV cavity, improved contractility and relaxation, less collagen I mRNA, increased endothelial nitric oxide synthase (NOS) production, and decreased peroxynitrite accumulation (98). Similar studies in post-MI mice treated with fluvastatin showed improved survival, decreased LV volume, improved LV ejection fraction, and decreased matrix metalloproteinase (MMP)-2 and 13 activity. These findings suggest that fluvastatin, and maybe all statins, can improve LV remodeling through inhibition of MMPs that are known to cause infarct expansion and LV dilatation (99).

Statins are also known to improve endothelial dysfunction; the mechanism is nitric oxide dependent. Similarly, the nitric oxide (NO) enhancing properties of statins may also be implicated in LV remodeling. Nahrendorf et al. treated post-MI mice with cerivastatin, and analysis by cardiac MRI showed decreased hypertrophy and decreased LV cavity size. Interestingly, the protective effect of cerivastatin was mostly abolished by the addition of N-methyl-L-arginine methyl ester (L-NAME), which is an inhibitor of NOS (100). This suggests an important role for NO and NOS in the statin-mediated protection against LV remodeling. Similar beneficial effects on LV remodeling via a NOS/NO-dependent pathway were demonstrated with atorvastatin in mice, thus strengthening the argument for a class effect of statins (101). In the present era, when it would be difficult to withhold statins after an MI, there will probably be no large randomized trial to fully determine whether the experimental benefits in remodeling translate to the patient.

Revascularization

Modern care dictates that in acute myocardial infarctions, the occluded artery should be opened as soon as possible, in order to optimize myocardial salvage and improve mortality (102, 103). This has

clearly been shown to reduce infarct size and improve hemodynamic measurements of LV function (104). There is some debate as to whether reperfusing an artery that is out of the typical range of thrombolytic therapy has any important clinical implications, the so called “open-artery hypothesis.”

There have been several studies to evaluate whether late reperfusion has any important clinical benefits. Investigators were encouraged when a subgroup analysis of ISIS-3 Trial patients who received thrombolytic therapy between 5 and 24 hours after MI showed a 33% mortality benefit (105). The benefits were thought to be the same as with early revascularization: improved electrical stability, less scar formation, preserved ejection fraction, and less ventricular remodeling. Several small trials have attempted to evaluate the effect of late reperfusion on EF and LV size. Gil et al. evaluated 103 patients randomized to alteplase or placebo 6–24 hours after an MI. Interestingly, there was a more improved EF at 1 month, but no difference by 6 months (104). Topol et al. found similarly conflicting results in 197 patients enrolled in the TAMI-6 trial, who also presented late. LV volumes were preserved, but there was no significant effect on ejection fraction (106). Other trials have had similar unimpressive results (107). Despite the scarcity of evidence of improvement, opening coronary arteries late after the infarct is a relatively common practice.

The Future

Inhibition and blockade of various enzymes and receptors in the RAAS pathway has been the basis of therapy to inhibit LV remodeling to date. There are, however, promising therapies using other modalities. Regeneration of the myocardium has been a “hot topic” paralleling the interest in stem cells. Several different ways to effect new tissue growth are being studied in early clinical trials. Surgical approaches to inhibit remodeling have also been looked at. The CorCap™ device (Acorn Vascular, Inc., St. Paul, MN) has been used with some success in humans with chronic CHF, and is now being evaluated in animals after MI. Another promising therapy involves pacing the left ventricle. The benefits of biventricular pacing have been shown in chronic heart failure; it is now time to investigate its role in post-MI patients.

Cell Therapy

Therapy aimed at modifying the scar left after a myocardial infarction has included experimental cell-based therapies. Initial studies implanted

skeletal muscle myoblasts into the scarred region. The myoblasts implanted, but clinical studies revealed unacceptably high rates of ventricular tachycardia and sudden death (108, 109). Indeed, further trials have required the use of amiodarone or an implantable cardiac defibrillator to enroll patients. Observations that adult cardiomyocytes were capable of being replaced by progenitor cells have led to speculation that both bone-marrow-derived and embryonic stem cells may be more effective than skeletal muscle myoblasts (110).

In 2004, the results of TOPCARE-AMI were published; they looked promising. Fifty-nine patients with an acute MI were randomized to intracoronary infusions of circulating progenitor cells or bone-marrow-derived progenitor cells 5 days after the MI. Although it was only a pilot study, at one year it appeared safe to infuse either type of cell, and LV volumes and EF were similar in both (111). As an alternative to direct coronary infusion, the induction of bone marrow progenitor cells by granulocyte-colony stimulating factor (G-CSF) was evaluated as another way to increase the number of progenitor cells in the circulation (112). Unfortunately a small pilot study with 27 patients in Korea showed an increase in coronary restenosis when G-CSF was used (113). This was followed by a larger study of 50 patients in the FIRSTLINE-AMI trial, who were given G-CSF 90 minutes after percutaneous coronary intervention (PCI) for acute MI. Follow-up data on those patients did not reveal accelerated restenosis, and left ventricular size and function were significantly improved at 4 months (114). Another trial, REPAIR-AMI, enrolled 204 patients for a multicenter study that infused autologous bone marrow cells into patients 3–5 days after they underwent primary PCI for an acute MI; the data were presented at the AHA last year (115). The ASTAMI investigators used intracoronary injection of bone marrow cells in 101 patients with anterior wall MI. Six-month data was presented at the recent AHA meeting (116). Despite the early setbacks, it appears that there will be further studies to determine the right type of cell therapy to prevent post-MI LV remodeling through tissue regeneration.

Surgical Restraint Device

The idea of using a restraining wrap or device to prevent LV dilatation and even shrink cavity size presents another way in which to prevent remodeling. A randomized trial using a synthetic mesh (CorCap™) in patients with advanced CHF undergoing mitral valve surgery demonstrated some reduction in LV size and patient symptoms (117). In the post-MI setting there have been

promising animal studies (in sheep) that have shown that the passive restraint device can decrease infarct expansion, improve cardiac function, and interrupt LV remodeling (118, 119). However, until this device can be deployed through a minimally invasive technique, it is unlikely to gain much popularity.

Pacing

Cardiac resynchronization therapy has proven useful for advanced heart failure patients with conduction system disease. It has long been known that electrical dyssynchrony is accompanied by mechanical dyssynchrony. A number of clinical trials have now shown that the placement of bi-ventricular pacemakers improves clinical outcomes, including mortality and morbidity (120). The mechanism for the benefit includes improved contractile function, reduced mitral regurgitation, improved energy utilization, and reverse remodeling (121–123). With the strength of data emerging in favor of resynchronization therapy for chronic heart failure, perhaps the same concepts can prove useful in preventing heart failure after MI.

In pre-clinical studies of left bundle branch block and right ventricular pacing, there have been differences in the myocardial work, nutrient balance, and remodeling related to the proximity to the pacing site (124–126). The myocardium closer to the site of pacing does less work than the more distant myocardium. In the therapy of CHF, bi-ventricular pacing has been found to improve mortality, morbidity and quality of life, and effect reverse remodeling (127–129). If these benefits could be extended to patients with significant anterior wall MIs to prevent remodeling, it would have an important clinical impact on post-MI survival. There is the possibility of having early clinical testing, and preliminary results should be available within 18 months. The study will enroll 60 patients with an anterior MI with creatine phosphokinase of at least 2,000 U/L. The patients will undergo bi-ventricular pacing with the LV lead placed close to the infarct zone. In theory, the infarct zone myocardium will be required to do less work and perhaps undergo less remodeling. If this pacing has benefits when added to ACE inhibition, beta-blockers, and other neurohormonal blockade, then it may have a prominent role in post-MI therapy.

Conclusions

It is clear that new therapies are urgently needed to curtail the progression from myocardial infarction to end-stage heart failure. The most ef-

fective therapies will likely be ones that are initiated immediately after an acute MI before long-term changes occur. Until the time comes when we have a single option that is cost effective with no detrimental effects, we will need to use the existing tools that we have. While ACE inhibitors and beta-blockers are being extensively used after an MI, the addition of aldosterone antagonism is lagging behind, due to well-founded physician fears of hyperkalemia and renal dysfunction (130). The near future may bring device-driven pacing therapy or even minimally invasive surgical restraint devices.

References

1. Know the facts, get the stats. American Heart Association, 2005.
2. McKay RG, Pfeffer MA, Pasternak RC, et al. Left ventricular remodeling after myocardial infarction: a corollary to infarct expansion. *Circulation* 1986; 74:693–702.
3. Heart Disease and Stroke Statistics—2005 Update. American Heart Association Website, 2005.
4. Pfeffer MA, Braunwald E. Ventricular remodeling after myocardial infarction. Experimental observations and clinical implications. *Circulation* 1990; 81:1161–1172.
5. Sutton MG, Sharpe N. Left ventricular remodeling after myocardial infarction: pathophysiology and therapy. *Circulation* 2000; 101:2981–2988.
6. Cohn JN, Ferrari R, Sharpe N. Cardiac remodeling—concepts and clinical implications: a consensus paper from an international forum on cardiac remodeling. Behalf of an International Forum on Cardiac Remodeling. *J Am Coll Cardiol* 2000; 35:569–582.
7. Pfeffer JM, Pfeffer MA, Fletcher PJ, Braunwald E. Progressive ventricular remodeling in rat with myocardial infarction. *Am J Physiol* 1991; 260:H1406–1414.
8. Weisman HF, Bush DE, Mannisi JA, et al. Cellular mechanisms of myocardial infarct expansion. *Circulation* 1988; 78:186–201.
9. Weisman HF, Healy B. Myocardial infarct expansion, infarct extension, and reinfarction: pathophysiologic concepts. *Prog Cardiovasc Dis* 1987; 30:73–110.
10. Warren SE, Royal HD, Markis JE, et al. Time course of left ventricular dilation after myocardial infarction: influence of infarct-related artery and success of coronary thrombolysis. *J Am Coll Cardiol* 1988; 11:12–19.
11. Lamas GA, Pfeffer MA. Increased left ventricular volume following myocardial infarction in man. *Am Heart J* 1986; 111:30–35.
12. Mitchell GF, Lamas GA, Vaughan DE, Pfeffer MA. Left ventricular remodeling in the year after first anterior myocardial infarction: a quantitative analysis of contractile segment lengths and ventricular shape. *J Am Coll Cardiol* 1992; 19:1136–1144.
13. Mitchell GF, Lamas GA, Pfeffer MA. Ventricular remodeling after myocardial infarction. *Adv Exp Med Biol* 1993; 346:265–276.
14. Burton AC. The importance of the shape and size of the heart. *Am Heart J* 1957; 54:801–810.
15. Aikawa Y, Rohde L, Plehn J, et al. Regional wall stress predicts ventricular remodeling after anteroapical myocardial infarction in the Healing and Early Afterload Reducing Trial (HEART): an echocardiography-based structural analysis. *Am Heart J* 2001; 141:234–242.
16. Fu YC, Chi CS, Yin SC, et al. Norepinephrine induces apoptosis in neonatal rat cardiomyocytes through a reactive oxygen species-TNF alpha-caspase signaling pathway. *Cardiovasc Res* 2004; 62(2):558–567.
17. Wagner A, Mahrholdt H, Holly TA, et al. Contrast-enhanced MRI and routine single photon emission computed tomography (SPECT) perfusion imaging for detection of subendocardial myocardial infarcts: an imaging study. *Lancet* 2003; 361:374–379.
18. Wu KC, Zerhouni EA, Judd RM, et al. Prognostic significance of microvascular obstruction by magnetic resonance imaging in patients with acute myocardial infarction. *Circulation* 1998; 97:765–772.
19. Taylor AJ, Al-Saadi N, Abdel-Aty H, et al. Detection of acutely impaired microvascular reperfusion after infarct angioplasty with magnetic resonance imaging. *Circulation* 2004; 109:2080–2085.
20. Jugdutt BI. Nitrates for myocardial salvage in the 1990s. *Cardiology* 1991; 79 Suppl 2:2–4.
21. Jugdutt BI. Intravenous nitroglycerin unloading in acute myocardial infarction. *Am J Cardiol* 1991; 68:52D–63D.
22. Jugdutt BI, Warnica JW. Intravenous nitroglycerin therapy to limit myocardial infarct size, expansion, and complications. Effect of timing, dosage, and infarct location. *Circulation* 1988; 78:906–919.
23. Ruiz-Stewart I, Tiyyagura SR, Lin JE, et al. Guanylyl cyclase is an ATP sensor coupling nitric oxide signaling to cell metabolism. *Proc Natl Acad Sci U S A* 2004; 101:37–42.
24. Tiyyagura SR, Kazerounian S, Schulz S, et al. Reciprocal regulation and integration of signaling by intracellular calcium and cyclic GMP. *Vitam Horm* 2004; 69:69–94.
25. Ignarro LJ, Lippton H, Edwards JC, et al. Mechanism of vascular smooth muscle relaxation by organic nitrates, nitrites, nitroprusside and nitric oxide: evidence for the involvement of S-nitrosothiols as active intermediates. *J Pharmacol Exp Ther* 1981; 218:739–749.
26. Jugdutt BI. Myocardial salvage by intravenous nitroglycerin in conscious dogs: loss of beneficial effect with marked nitroglycerin-induced hypotension. *Circulation* 1983; 68:673–684.
27. Come PC, Flaherty JT, Baird MG, et al. Reversal by phenylephrine of the beneficial effects of intravenous nitroglycerin in patients with acute myocardial infarction. *N Engl J Med* 1975; 293:1003–1007.
28. Six-month effects of early treatment with lisinopril and transdermal glyceryl trinitrate singly and together withdrawn six weeks after acute myocardial infarction: the GISSI-3 trial. Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico. *J Am Coll Cardiol* 1996; 27:337–344.
29. Yusuf S, Collins R, MacMahon S, Peto R. Effect of intravenous nitrates on mortality in acute myocardial infarction: an overview of the randomised trials. *Lancet* 1988; 1:1088–1092.
30. ISIS-4: a randomised factorial trial assessing early oral captopril, oral mononitrate, and intravenous magnesium sulphate in 58,050 patients with suspected acute myocardial infarction. ISIS-4 (Fourth International Study of Infarct Survival) Collaborative Group. *Lancet* 1995; 345:669–685.
31. Antman EM, Anbe DT, Armstrong PW, et al. ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1999 Guidelines for the Management of Patients with Acute Myocardial Infarction). *Circulation* 2004; 110:e82–e292.

32. Pueyo ME, Michel JB. Angiotensin II receptors in endothelial cells. *Gen Pharmacol* 1997; 29:691–696.
33. Clemson B, Gaul L, Gubin SS, et al. Prejunctional angiotensin II receptors. Facilitation of norepinephrine release in the human forearm. *J Clin Invest* 1994; 93:684–691.
34. Pellieux C, Foletti A, Peduto G, et al. Dilated cardiomyopathy and impaired cardiac hypertrophic response to angiotensin II in mice lacking FGF-2. *J Clin Invest* 2001; 108:1843–1851.
35. Harrap SB, Dominiczak AF, Fraser R, et al. Plasma angiotensin II, predisposition to hypertension, and left ventricular size in healthy young adults. *Circulation* 1996; 93:1148–1154.
36. Pinto YM, de Smet BG, van Gilst WH, et al. Selective and time related activation of the cardiac renin-angiotensin system after experimental heart failure: relation to ventricular function and morphology. *Cardiovasc Res* 1993; 27:1933–1938.
37. Pfeffer JM, Pfeffer MA, Mirsky I, Braunwald E. Regression of left ventricular hypertrophy and prevention of left ventricular dysfunction by captopril in the spontaneously hypertensive rat. *Proc Natl Acad Sci U S A* 1982; 79:3310–3314.
38. Pfeffer JM, Pfeffer MA, Mirsky I, Braunwald E. Prevention of the development of heart failure and the regression of cardiac hypertrophy by captopril in the spontaneously hypertensive rat. *Eur Heart J* 1983; 4 Suppl A:143–148.
39. Brilla CG, Reams GP, Maisch B, Weber KT. Renin-angiotensin system and myocardial fibrosis in hypertension: regulation of the myocardial collagen matrix. *Eur Heart J* 1993; 14 Suppl J:57–61.
40. Pfeffer MA, Lamas GA, Vaughan DE, et al. Effect of captopril on progressive ventricular dilatation after anterior myocardial infarction. *N Engl J Med* 1988; 319:80–86.
41. Sharpe N, Murphy J, Smith H, Hannan S. Treatment of patients with symptomless left ventricular dysfunction after myocardial infarction. *Lancet* 1988; 1:255–259.
42. Pfeffer MA, Braunwald E, Moye LA, et al. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. Results of the survival and ventricular enlargement trial. The SAVE Investigators. *N Engl J Med* 1992; 327:669–677.
43. Kober L, Torp-Pedersen C, Carlsen JE, et al. A clinical trial of the angiotensin-converting-enzyme inhibitor trandolapril in patients with left ventricular dysfunction after myocardial infarction. Trandolapril Cardiac Evaluation (TRACE) Study Group. *N Engl J Med* 1995; 333:1670–1676.
44. Latini R, Tognoni G, Maggioni AP, et al. Clinical effects of early angiotensin-converting enzyme inhibitor treatment for acute myocardial infarction are similar in the presence and absence of aspirin: systematic overview of individual data from 96,712 randomized patients. Angiotensin-converting Enzyme Inhibitor Myocardial Infarction Collaborative Group. *J Am Coll Cardiol* 2000; 35:1801–1807.
45. Flather MD, Yusuf S, Kober L, et al. Long-term ACE-inhibitor therapy in patients with heart failure or left-ventricular dysfunction: a systematic overview of data from individual patients. ACE-Inhibitor Myocardial Infarction Collaborative Group. *Lancet* 2000; 355:1575–1581.
46. Rodrigues EJ, Eisenberg MJ, Pilote L. Effects of early and late administration of angiotensin-converting enzyme inhibitors on mortality after myocardial infarction. *Am J Med* 2003; 115:473–479.
47. Swedberg K, Held P, Kjeksus J, et al. Effects of the early administration of enalapril on mortality in patients with acute myocardial infarction. Results of the Cooperative New Scandinavian Enalapril Survival Study II (CONSENSUS II). *N Engl J Med* 1992; 327:678–684.
48. Zornoff LA, Paiva SA, Matsubara BB, et al. Combination therapy with angiotensin converting enzyme inhibition and AT1 receptor inhibitor on ventricular remodeling after myocardial infarction in rats. *J Cardiovasc Pharmacol Ther* 2000; 5:203–209.
49. Nakamura Y, Yoshiyama M, Omura T, et al. Beneficial effects of combination of ACE inhibitor and angiotensin II type 1 receptor blocker on cardiac remodeling in rat myocardial infarction. *Cardiovasc Res* 2003; 57:48–54.
50. Zhang G, Shen X, Pu S, et al. Comparative effects of losartan and captopril on ventricular remodeling and function after myocardial infarction in the rat. *Chin Med Sci J* 1998; 13:32–36.
51. Mankad S, d'Amato TA, Reichek N, et al. Combined angiotensin II receptor antagonism and angiotensin-converting enzyme inhibition further attenuates postinfarction left ventricular remodeling. *Circulation* 2001; 103:2845–2850.
52. Wolny A, Clozel JP, Rein J, et al. Functional and biochemical analysis of angiotensin II-forming pathways in the human heart. *Circ Res* 1997; 80:219–227.
53. van Kats JP, Danser AH, van Meegen Jret al. Angiotensin production by the heart: a quantitative study in pigs with the use of radiolabeled angiotensin infusions. *Circulation* 1998; 98:73–81.
54. Roig E, Perez-Villa F, Morales M, et al. Clinical implications of increased plasma angiotensin II despite ACE inhibitor therapy in patients with congestive heart failure. *Eur Heart J* 2000; 21:53–57.
55. Horiuchi M, Akishita M, Dzau VJ. Recent progress in angiotensin II type 2 receptor research in the cardiovascular system. *Hypertension* 1999; 33:613–621.
56. Dickstein K, Kjeksus J. Effects of losartan and captopril on mortality and morbidity in high-risk patients after acute myocardial infarction: the OPTIMAAL randomised trial. Optimal Trial in Myocardial Infarction with Angiotensin II Antagonist Losartan. *Lancet* 2002; 360:752–760.
57. Pfeffer MA, McMurray JJ, Velazquez EJ, et al. Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both. *N Engl J Med* 2003; 349:1893–1906.
58. Solomon SD, Skali H, Anavekar NS, et al. Changes in ventricular size and function in patients treated with valsartan, captopril, or both after myocardial infarction. *Circulation* 2005; 111:3411–3419.
59. Weber KT, Sun Y, Tyagi SC, Cleutjens JP. Collagen network of the myocardium: function, structural remodeling and regulatory mechanisms. *J Mol Cell Cardiol* 1994; 26:279–292.
60. Dzau VJ. Mechanism of protective effects of ACE inhibition on coronary artery disease. *Eur Heart J* 1998; 19 Suppl J:J2–J6.
61. Dzau VJ, Colucci WS, Hollenberg NK, Williams GH. Relation of the renin-angiotensin-aldosterone system to clinical state in congestive heart failure. *Circulation* 1981; 63:645–651.
62. Struthers AD. Aldosterone escape during angiotensin-converting enzyme inhibitor therapy in chronic heart failure. *J Card Fail* 1996; 2:47–54.
63. Borghi C, Boschi S, Ambrosioni E, et al. Evidence of a partial escape of renin-angiotensin-aldosterone blockade in patients with acute myocardial infarction treated with ACE inhibitors. *J Clin Pharmacol* 1993; 33:40–55.
64. Weber KT, Brilla CG, Campbell SE, et al. Myocardial fibrosis: role of angiotensin II and aldosterone. *Basic Res Cardiol* 1993; 88 Suppl 1:107–124.
65. Weber KT, Villarreal D. Aldosterone and antialdosterone therapy in congestive heart failure. *Am J Cardiol* 1993; 71(3):3A–11A.

66. Weber KT, Villarreal D. Role of aldosterone in congestive heart failure. *Postgrad Med* 1993; 93(5):203–7, 211–2, 216–218 passim.
67. Brilla CG, Matsubara LS, Weber KT. Anti-aldosterone treatment and the prevention of myocardial fibrosis in primary and secondary hyperaldosteronism. *J Mol Cell Cardiol* 1993; 25:563–575.
68. Pitt B, Zannad F, Remme WJ, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. *N Engl J Med* 1999; 341:709–717.
69. Zannad F, Alla F, Dousset B, et al. Limitation of excessive extracellular matrix turnover may contribute to survival benefit of spironolactone therapy in patients with congestive heart failure: insights from the randomized aldactone evaluation study (RALES). Rales Investigators. *Circulation* 2000; 102(22):2700–2706. Erratum in: *Circulation* 2001; 103(3):476.
70. Ciccoira M, Zanolla L, Rossi A, et al. Long-term, dose-dependent effects of spironolactone on left ventricular function and exercise tolerance in patients with chronic heart failure. *J Am Coll Cardiol* 2002; 40:304–310.
71. Rajagopalan S, Duquaine D, King S, et al. Mineralocorticoid receptor antagonism in experimental atherosclerosis. *Circulation* 2002; 105:2212–2216.
72. Pitt B, Remme W, Zannad F, et al. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med* 2003; 348:1309–1321.
73. Antman EM, Anbe DT, Armstrong PW, et al. ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction; A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1999 Guidelines for the Management of patients with acute myocardial infarction). *J Am Coll Cardiol* 2004; 44:E1–E211.
74. Ryden L, Ariniego R, Arnman K, et al. A double-blind trial of metoprolol in acute myocardial infarction. Effects on ventricular tachyarrhythmias. *N Engl J Med* 1983; 308:614–618.
75. Friedman LM, Byington RP, Capone RJ, et al. Effect of propranolol in patients with myocardial infarction and ventricular arrhythmia. *J Am Coll Cardiol* 1986; 7:1–8.
76. Timolol-induced reduction in mortality and reinfarction in patients surviving acute myocardial infarction. *N Engl J Med* 1981; 304:801–807.
77. Colucci WS, Packer M, Bristow MR, et al. Carvedilol inhibits clinical progression in patients with mild symptoms of heart failure. US Carvedilol Heart Failure Study Group. *Circulation* 1996; 94:2800–2806.
78. Packer M, Colucci WS, Sackner-Bernstein JD, et al. Double-blind, placebo-controlled study of the effects of carvedilol in patients with moderate to severe heart failure. The PRECISE Trial. Prospective Randomized Evaluation of Carvedilol on Symptoms and Exercise. *Circulation* 1996; 94:2793–2799.
79. Packer M, Bristow MR, Cohn JN, et al. The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. U.S. Carvedilol Heart Failure Study Group. *N Engl J Med* 1996; 334:1349–1355.
80. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). *Lancet* 1999; 353:2001–2007.
81. Senior R, Basu S, Kinsey C, et al. Carvedilol prevents remodeling in patients with left ventricular dysfunction after acute myocardial infarction. *Am Heart J* 1999; 137:646–652.
82. Basu S, Senior R, Raval U, et al. Beneficial effects of intravenous and oral carvedilol treatment in acute myocardial infarction. A placebo-controlled, randomized trial. *Circulation* 1997; 96:183–191.
83. Dargie HJ. Effect of carvedilol on outcome after myocardial infarction in patients with left-ventricular dysfunction: the CAPRICORN randomised trial. *Lancet* 2001; 357:1385–1390.
84. Doughty RN, Whalley GA, Walsh HA, et al. Effects of carvedilol on left ventricular remodeling after acute myocardial infarction: the CAPRICORN Echo Substudy. *Circulation* 2004; 109:201–206.
85. Chen ZM, Pan HC, Chen YP, et al. Early intravenous then oral metoprolol in 45,852 patients with acute myocardial infarction: randomised placebo-controlled trial. *Lancet* 2005; 366:1622–1632.
86. Li B, Liao YH, Cheng X, et al. Effects of carvedilol on cardiac cytokines expression and remodeling in rat with acute myocardial infarction. *Int J Cardiol* 2005; doi:10.1016/j.ijcard.2005.08.065.
87. Bristow MR. beta-adrenergic receptor blockade in chronic heart failure. *Circulation* 2000; 101:558–569.
88. Plank DM, Yatani A, Ritsu H, et al. Calcium dynamics in the failing heart: restoration by beta-adrenergic receptor blockade. *Am J Physiol Heart Circ Physiol* 2003; 285:H305–H315.
89. Hasenfuss G, Reinecke H, Studer R, et al. Relation between myocardial function and expression of sarcoplasmic reticulum Ca(2+)-ATPase in failing and nonfailing human myocardium. *Circ Res* 1994; 75:434–442.
90. Sun YL, Hu SJ, Wang LH, et al. Effect of beta-blockers on cardiac function and calcium handling protein in postinfarction heart failure rats. *Chest* 2005; 128(3):1812–1821.
91. Ray KK, Cannon CP. Early time to benefit with intensive statin treatment: could it be the pleiotropic effects? *Am J Cardiol* 2005; 96:54F–60F.
92. Rosenson RS, Tangney CC. Antiatherothrombotic properties of statins: implications for cardiovascular event reduction. *JAMA* 1998; 279:1643–1650.
93. de Lemos JA, Blazing MA, Wiviott SD, et al. Early intensive vs a delayed conservative simvastatin strategy in patients with acute coronary syndromes: phase Z of the A to Z trial. *JAMA* 2004; 292(11):1307–1316.
94. Cannon CP, Braunwald E, McCabe CH, et al. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. *N Engl J Med* 2004; 350:1495–1504.
95. Schwartz GG, Olsson AG, Ezekowitz MD, et al. Effects of atorvastatin on early recurrent ischemic events in acute coronary syndromes: the MIRACL study: a randomized controlled trial. *JAMA* 2001; 285:1711–1718.
96. Zhang J, Cheng X, Liao YH, et al. Simvastatin regulates myocardial cytokine expression and improves ventricular remodeling in rats after acute myocardial infarction. *Cardiovasc Drugs Ther* 2005; 19:13–21.
97. Martin J, Denver R, Bailey M, Krum H. In vitro inhibitory effects of atorvastatin on cardiac fibroblasts: implications for ventricular remodeling. *Clin Exp Pharmacol Physiol* 2005; 32:697–701.
98. Bauersachs J, Galuppo P, Fraccarollo D, et al. Improvement of left ventricular remodeling and function by hydroxymethylglutaryl coenzyme a reductase inhibition with cerivastatin in rats with heart failure after myocardial infarction. *Circulation* 2001; 104:982–985.
99. Hayashidani S, Tsutsui H, Shiomi T, et al. Fluvastatin, a 3-hydroxy-3-methylglutaryl coenzyme a reductase inhibitor, attenuates left ventricular remodeling and failure after experimental myocardial infarction. *Circulation* 2002; 105:868–873.

100. Nahrendorf M, Hu K, Hiller KH, et al. Impact of hydroxymethylglutaryl coenzyme a reductase inhibition on left ventricular remodeling after myocardial infarction: an experimental serial cardiac magnetic resonance imaging study. *J Am Coll Cardiol* 2002; 40:1695–1700.
101. Landmesser U, Engberding N, Bahlmann FH, et al. Statin-induced improvement of endothelial progenitor cell mobilization, myocardial neovascularization, left ventricular function, and survival after experimental myocardial infarction requires endothelial nitric oxide synthase. *Circulation* 2004; 110:1933–1939.
102. [GUSTO (Global Utilization of Streptokinase & t-PA for Occluded Coronary Arteries): comparison of four therapeutic strategies in acute myocardial infarction. Washington, 30 April 1993]. [German] *Internist (Berl)* 1993; 34(7 Suppl):1–12.
103. Topol EJ. Validation of the early open infarct vessel hypothesis. *Am J Cardiol* 1993; 72:40G–45G.
104. Gil VM, Ventosa A, Antunes Afet al. Left ventricular function after late thrombolysis with alteplase in myocardial infarction. *Rev Port Cardiol* 1996; 15:413–420, 366.
105. Randomised trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected acute myocardial infarction: ISIS-2. ISIS-2 (Second International Study of Infarct Survival) Collaborative Group. *Lancet* 1988; 2:349–360.
106. Topol EJ, Califf RM, Vandormael M, et al. A randomized trial of late reperfusion therapy for acute myocardial infarction. Thrombolysis and Angioplasty in Myocardial Infarction-6 Study Group. *Circulation* 1992; 85:2090–2099.
107. Dzavik V. New frontiers and unresolved controversies in percutaneous coronary intervention. *Am J Cardiol* 2003; 91:27A–33A.
108. Menasche P, Hagege AA, Vilquin JT, et al. Autologous skeletal myoblast transplantation for severe postinfarction left ventricular dysfunction. *J Am Coll Cardiol* 2003; 41:1078–1083.
109. Smits PC, van Geuns RJ, Poldermans D, et al. Catheter-based intramyocardial injection of autologous skeletal myoblasts as a primary treatment of ischemic heart failure: clinical experience with six-month follow-up. *J Am Coll Cardiol* 2003; 42:2063–2069.
110. Quaini F, Urbanek K, Beltrami AP, et al. Chimerism of the transplanted heart. *N Engl J Med* 2002; 346:5–15.
111. Schachinger V, Assmus B, Britten MB, et al. Transplantation of progenitor cells and regeneration enhancement in acute myocardial infarction: final one-year results of the TOP-CARE-AMI Trial. *J Am Coll Cardiol* 2004; 44:1690–1699.
112. Bensinger WI, Clift RA, Anasetti C, et al. Transplantation of allogeneic peripheral blood stem cells mobilized by recombinant human granulocyte colony stimulating factor. *Stem Cells* 1996; 14:90–105.
113. Kang HJ, Kim HS, Zhang SY, et al. Effects of intracoronary infusion of peripheral blood stem-cells mobilised with granulocyte-colony stimulating factor on left ventricular systolic function and restenosis after coronary stenting in myocardial infarction: the MAGIC cell randomised clinical trial. *Lancet* 2004; 363:751–756.
114. Ince H, Petsch M, Kleine HD, et al. Preservation from left ventricular remodeling by front-integrated revascularization and stem cell liberation in evolving acute myocardial infarction by use of granulocyte-colony-stimulating factor (FIRST-LINE-AMI). *Circulation* 2005; 112:3097–3106.
115. Schachinger V, et al. Intracoronary infusion of bone marrow-derived progenitor cells in acute myocardial infarction: a randomized, double-blind, placebo-controlled multicenter trial (REPAIR-AMI). American Heart Association Scientific Sessions. Nov 13–16, 2005; Dallas, TX.
116. Lunde K, et al. Effects on left ventricular function by intracoronary injections of autologous mononuclear bone marrow cells in acute anterior wall myocardial: the ASTAMI randomized controlled trial. American Heart Association Scientific Sessions. Nov 13–16; Dallas, TX.
117. Oz MC, Konertz WF, Kleber FX, et al. Global surgical experience with the Acorn cardiac support device. *J Thorac Cardiovasc Surg* 2003; 126(4):983–991.
118. Blom AS, Pilla JJ, Gorman RC, 3rd, et al. Infarct size reduction and attenuation of global left ventricular remodeling with the CorCap(TM) cardiac support device following acute myocardial infarction in sheep. *Heart Fail Rev* 2005; 10:125–139.
119. Blom AS, Mukherjee R, Pilla JJ, et al. Cardiac support device modifies left ventricular geometry and myocardial structure after myocardial infarction. *Circulation* 2005; 112:1274–1283.
120. Cleland JG, Daubert JC, Erdmann E, et al. Baseline characteristics of patients recruited into the CARE-HF study. *Eur J Heart Fail* 2005; 7:205–214.
121. Chan KL, Tang AS, Achilli A, et al. Functional and echocardiographic improvement following multisite biventricular pacing for congestive heart failure. *Can J Cardiol* 2003; 19:387–390.
122. St John Sutton MG, Plappert T, Abraham WT, et al. Effect of cardiac resynchronization therapy on left ventricular size and function in chronic heart failure. *Circulation* 2003; 107:1985–1990.
123. Ukkonen H, Beanlands RS, Burwash IG, et al. Effect of cardiac resynchronization on myocardial efficiency and regional oxidative metabolism. *Circulation* 2003; 107:28–31.
124. Beppu S, Matsuda H, Shishido T, Miyatake K. Functional myocardial perfusion abnormality induced by left ventricular asynchronous contraction: experimental study using myocardial contrast echocardiography. *J Am Coll Cardiol* 1997; 29:1632–1638.
125. Prinzen FW, Cheriex EC, Delhaas T, et al. Asymmetric thickness of the left ventricular wall resulting from asynchronous electric activation: a study in dogs with ventricular pacing and in patients with left bundle branch block. *Am Heart J* 1995; 130:1045–1053.
126. Prinzen FW, Augustijn CH, Arts T, et al. Redistribution of myocardial fiber strain and blood flow by asynchronous activation. *Am J Physiol* 1990; 259:H300–H308.
127. Bradley DJ, Bradley EA, Baughman KL, et al. Cardiac resynchronization and death from progressive heart failure: a meta-analysis of randomized controlled trials. *JAMA* 2003; 289:730–740.
128. Bristow MR, Saxon LA, Boehmer J, et al. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. *N Engl J Med* 2004; 350:2140–2150.
129. Erol-Yilmaz A, Verberne HJ, Schrama TA, et al. Cardiac resynchronization induces favorable neurohumoral changes. *Pacing Clin Electrophysiol* 2005; 28:304–310.
130. Juurlink DN, Mamdani MM, Lee DS, et al. Rates of hyperkalemia after publication of the Randomized Aldactone Evaluation Study. *N Engl J Med* 2004; 351:543–551.