New Concepts in Post-Infarction Ventricular Remodeling

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An understanding of the process of left ventricular (LV) remodeling has led to greater knowledge of the pathophysiology of heart failure syndrome. This article examines the relationship between LV remodeling and clinical outcomes of heart failure syndrome from several different perspectives. The studies cited suggest that the post–myocardial infarction process is related to and associated with long-term progression of LV dysfunction, heart failure symptoms, and mortality. It is also demonstrated that drug therapies that slow or reverse the remodeling process appear to have favorable natural history effects in the short term as well as during long-term therapy.
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A major advance in understanding the pathophysiology of the heart failure syndrome has been an understanding of the process of left ventricular (LV) remodeling. Following any insult to the left ventricle resulting in diminished systolic performance and stroke volume, a series of histopathologic changes in the myocardium as well as structural changes in the LV chamber occurs over time.[1] Early work on understanding this process of LV remodeling emerged from the studies of Pfeffer and Braunwald[2] using a rat model

of myocardial infarction (MI). Compared to those with smaller MIs, rats with larger induced MIs underwent a substantially greater degree of chamber remodeling over time, and importantly, these structural changes were associated with significantly higher mortality. These studies established for the first time the relation between the structural changes now widely known as LV remodeling and a natural history outcome in the setting of LV systolic dysfunction. Subsequently, these investigators demonstrated that angiotensin-converting enzyme (ACE) inhibition with captopril, when initiated soon after the induced MI, attenuated the remodeling process.[3] Also observed was an improvement in survival among rats in which the remodeling process had been attenuated. These important data paved the way for human studies that subsequently provided substantial evidence to support two important concepts: that LV remodeling is related to clinical outcomes that represent the natural history of the heart failure syndrome, such as mortality, and that therapeutic interventions in humans that slow or reverse the process of LV remodeling, such as ACE inhibitors and ß-blockers, appear to have a favorable effect on that natural history.

This review examines the issue of the relation between LV remodeling and clinical outcomes in the human heart failure syndrome from several perspectives: a) the pathophysiology of ventricular remodeling and the role of the renin-angiotensin-aldosterone system (RAAS) and the sympathetic nervous system in ventricular remodeling, b) therapies used to treat and potentially reverse remodeling, and c) the relation between the effect of medical therapeutic interventions on the LV remodeling process and the effect of those same medical interventions on natural history outcomes in human heart failure.

Pathophysiology of Ventricular Remodeling and the Role of Neurohormonal Activation

LV remodeling refers to alterations in ventricular mass, chamber size, and shape that result from myocardial injury, or pressure or volume overload. At the cellular level, myocardial pathologic changes accompany LV remodeling and involve myocyte hypertrophy and fibroblast hyperplasia accompanied by an increase in collagen deposition within the interstitium. These processes, which occur in the noninfarcted myocardium, contribute to progressive LV remodeling and LV dysfunction. A substantial amount of experimental and clinical data now exist that support the pivotal role of the RAAS in contributing to these cellular processes.

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Angiotensin II (A-II) is formed locally within the myocardium and is known to be an important stimulus to these cellular events. Sadoshima and Izumo[4] demonstrated the localization of A-II within myocyte granules 30 minutes following mechanical stretch and showed that the increase in myocyte protein synthesis in response to mechanical stretch is largely blocked by an angiotensin type 1 (AT1) receptor antagonist. A-II also stimulates collagen production and proliferation of cardiac fibroblasts. These pivotal experimental data support the premise that the RAAS plays a central role in the pathophysiology of ventricular remodeling and heart failure progression.

Using a rat MI model, Taylor and colleagues[5] examined the effects of ACE inhibition and AT1 receptor blockade on nonmyocyte proliferation and collagen deposition within the noninfarct zone. In this study, ACE inhibition reduced nonmyocyte proliferation to levels comparable to those in sham animals. The AT1 receptor antagonist losartan also reduced nonmyocyte proliferation but to a lesser degree than the ACE inhibitor in this study. Similar results were observed for collagen content within the noninfarct zone. These somewhat disparate effects of ACE inhibition versus AT1 receptor blockade may result from an ACE inhibitor–mediated increase in local bradykinin levels, shown in some studies to be important to the growth inhibitory effects of ACE inhibitors. It is interesting that the combination of ACE inhibitor and AT1 receptor antagonist resulted in slightly greater effect (though not statistically different) in limiting collagen deposition, suggesting that the actions of the two agents may be additive.

Thus, these experimental data suggest that combination therapy directed against RAAS activation may be more effective in heart failure treatment and LV remodeling prevention. In addition, these data also support a pivotal role for the RAAS in the pathophysiology of post-MI progressive LV remodeling and underscore the importance of pharmacologic inhibition of the renin-angiotensin hormonal axis.

The mineralocorticoid aldosterone is yet another component of the RAAS that may significantly contribute to development of adverse ventricular

remodeling in patients with LV systolic dysfunction independent of effects of A-II. Aldosterone secretion has been shown to be partially under the control of A-II; however, multiple other factors influence the secretion of aldosterone, such as levels of sodium, potassium, adrenocorticotropic hormone, atrial natriuretic peptide, and endothelin.[6] Thus, inhibition of A-II formation by ACE inhibitors or blockade of AT1 receptors may not be sufficient to completely inhibit the secretion of aldosterone.

Aldosterone has been primarily implicated in the fibroblast responses within the myocardium that accompany remodeling of the left ventricle. In vitro, aldosterone induces an increase in collagen synthesis by cardiac fibroblasts.[7] In a rat MI model, Silvestre and colleagues[8] demonstrated that spironolactone partially inhibits the increase in interstitial collagen content within the noninfarcted myocardium. Thus, these data support the role of aldosterone in the fibroblast responses that accompany ventricular remodeling following myocardial injury and illuminate the importance of the interstitial response of the noninfarcted myocardium to the post-MI remodeling process.

The sympathetic nervous system may contribute to the post-MI remodeling process via a number of mechanisms, similar to the effects of the RAAS.

The role of sympathetic nervous system activation in directly promoting the process of post-MI LV remodeling has been somewhat less well studied. There are a substantial number of mechanisms whereby elevated levels of sympathetic system–derived neurohormones may unfavorably influence the remodeling process, either acutely or chronically, following MI. Besides promoting larger infarct size and greater propensity to remodeling on that basis, sympathetic nervous system activation will also enhance activation of the RAAS and promote unfavorable chronic loading conditions on the myocardium. Chronic adrenergic stimulation of the injured myocardium will also promote myocyte hypertrophy and later injury, altered signal transduction, and programmed cell death or apoptosis.[9]

Spyrou and colleagues[10] used noninvasive positron emission tomographic imaging to assess ß-adrenergic receptor density post-MI and its relation to remodeling. These investigators reported that in the 6 months after first acute MI, ß-adrenergic receptor density is decreased, particularly in myocardium remote from the infarct zone, which likely is related to increased sympathetic drive, and that the magnitude of receptor density reduction is directly related to the extent of post-MI remodeling. Activation of the sympathetic nervous system appears to promote myocardial production of cytokines, such as tumor necrosis factor (TNF)-α, interleukin (IL)-1ß, and IL-6.[11] These cytokines may also contribute independently to the remodeling process after myocardial injury through pathways such as promoting myocyte hypertrophy,[12] promoting apoptosis,[13] and inducing alterations in extracellular matrix in the myocardium, amplifying the unfavorable effects of the adrenergic nervous system and the RAAS.

Thus, the sympathetic nervous system may contribute to the post-MI remodeling process via a number of mechanisms, similar to the effects of the RAAS. All of these data together suggest that comprehensive neurohormonal blockade of the RAAS and of the sympathetic nervous system in the aftermath of MI should have favorable—and additive—effects on the process of LV remodeling.

Relation Between LV Volumes and Clinical Outcomes in LV Dysfunction

Since the early reports of the ability to determine LV volume by contrast angiography using invasive catheterization techniques[14] and subsequent reports validating ventricular volumetric calculations using noninvasive techniques such as radionuclide ventriculography[15] and echocardiography,[16] several reports have examined the relationship between LV volumes and long-term clinical outcomes in patients with LV dysfunction.

For example, the relation between cardiac size (reflected by the end-systolic volume index) has been examined in the post-MI population by Migrino and colleagues.[17] These investigators studied patients within 2–3 hours after MI who had been treated with thrombolytic reperfusion therapy. They found a continuous relationship between the end-systolic volume index and subsequent mortality (Figure 1). There was a similar relationship between LV end-systolic volume index and the risk for subsequent development of symptomatic heart failure during long-term follow-up. These data confirmed and extended earlier observations by White and coworkers,[18] who found that post-MI ejection fraction (measured at approximately 1–2 months post-MI) was a powerful predictor of prognosis in a large group of post-MI patients who had been treated with thrombolytic therapy. Moreover, within each ejec-

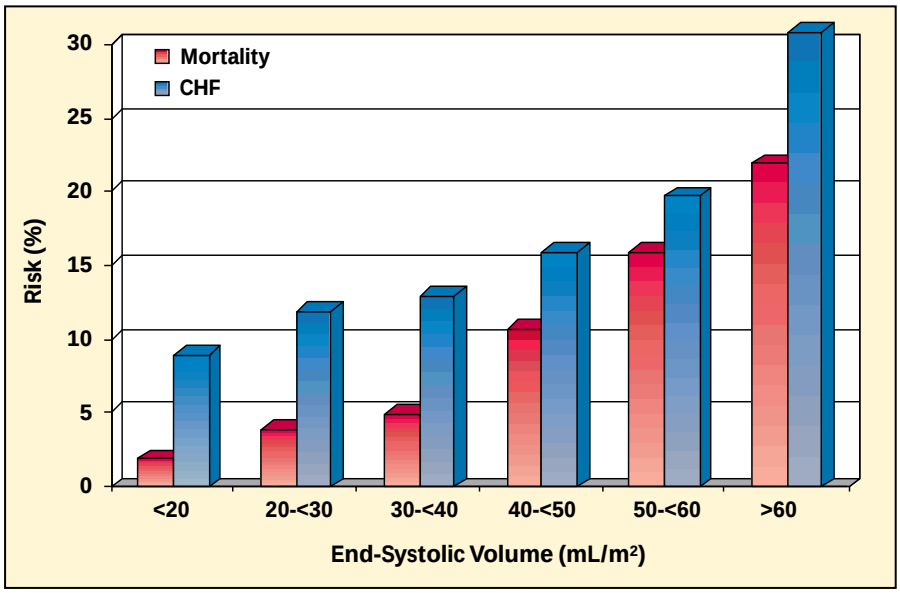


Figure 1. *The relation between end-systolic volume index (x-axis), measured by angiography soon after reperfused myocardial infarction, and risk of mortality, or developing symptomatic congestive heart failure (CHF) during long-term follow-up (y-axis). As end-systolic volume index increases, the probability of dying or developing heart failure also increases. Data from Migrino et al.*[17]

tion fraction tertile group post-MI, end-systolic volume index provided significantly more powerful risk stratification to determine which patients were at higher risk of subsequent adverse natural history. Thus, in the post-MI setting, a measurement of ejection fraction or end-systolic volume at one point in time in a population provides information regarding potential natural history outcomes; patients with lower ejection fraction and particularly larger ventricular volumes have substantially higher risk of death as well as of onset of symptomatic heart failure during follow-up.

The analogous issue was examined by Lee and colleagues[19] in a series of patients who had already developed symptomatic heart failure with established LV dysfunction. These investigators used a simple LV dimension index measurement from M-mode echocardiography (internal dimension at diastole/body surface area) and found that heart failure patients with an LV dimension index of >4 cm/m^2 were at significantly higher risk of 2-year-mortality than those with LV dimensions below that cut point. Patients with the larger ventricles in this dichotomous analysis had a 2 year-survival rate of only 49%, whereas those with smaller ventricles had 2-year survival of 75%. The dimension index was an independent predictor of survival.

These data, along with other studies examining ejection fraction alone for its prognostic ability in heart failure patients,[20] established that measurement of LV volume at one time point in the post-MI setting or in the setting of established heart failure can provide stratification regarding subsequent natural history. It should be noted that although the volumetric measurements appear to provide the most powerful data, ejection fraction measurements are simpler to obtain and are indeed a marker of the remodeling process. As LV volume enlarges, there tends to be a concomitant and usually parallel fall in ejection fraction, which thus can be used itself as a marker of the remodeling process. However, studies such as those of White and colleagues[18] emphasize that for any given ejection fraction range, LV volumetric measurements appear to provide incremental prognostic value.

LV Remodeling and Clinical Outcomes in Post-MI LV Dysfunction

Although many studies examine the effect of drug therapy on changes in LV volumes in ejection fraction, which can then be related to outcome events (see below), relatively few studies isolate the change in LV volume (the remodeling process) itself in order to examine its relation to natural history outcomes. One such study in which isolated remodeling data can be related to outcome events comes from a secondary analysis of the Survival and Ventricular Enlargement (SAVE) study. The parent SAVE trial[21] examined the effect of captopril on clinical outcomes in post-MI patients with LV ejection fraction (LVEF) ≤40% (by radionuclide ventriculography). Such patients were randomized to captopril at a target dose of 50 mg, tid, or to placebo, and the results confirmed those reported in the initial post-MI rat model studies, demonstrating a significant reduction in morbidity and mortality among patients randomized to receive captopril.

The effect of the ACE inhibitor on the remodeling process was initially examined in a subgroup of patients from the SAVE trial in whom serial quantitative evaluation of LV volumes demonstrated that treatment with captopril was associated with an attenuation of the process of LV enlargement that was observed in the placebo-treated patients.[22] In a subsequent analysis of a larger sub-

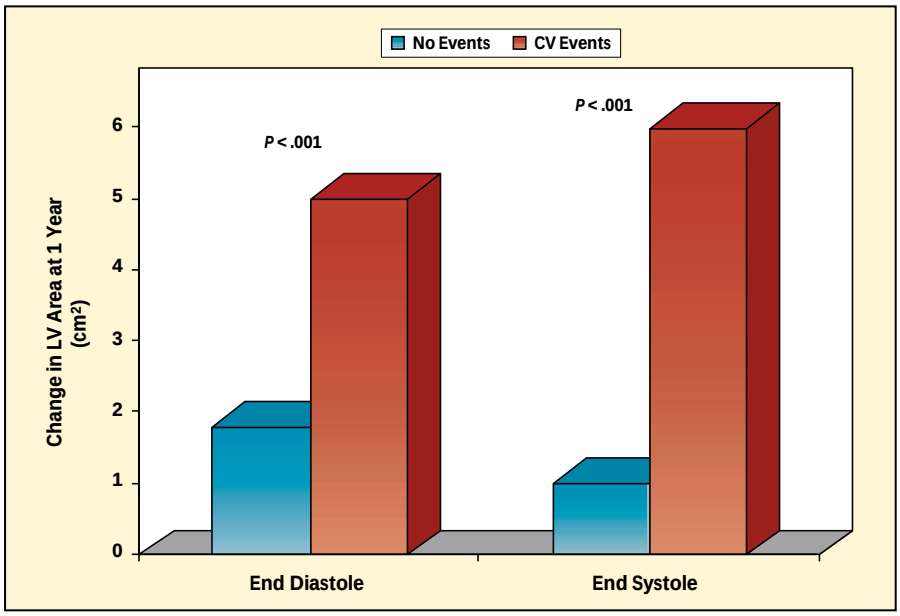


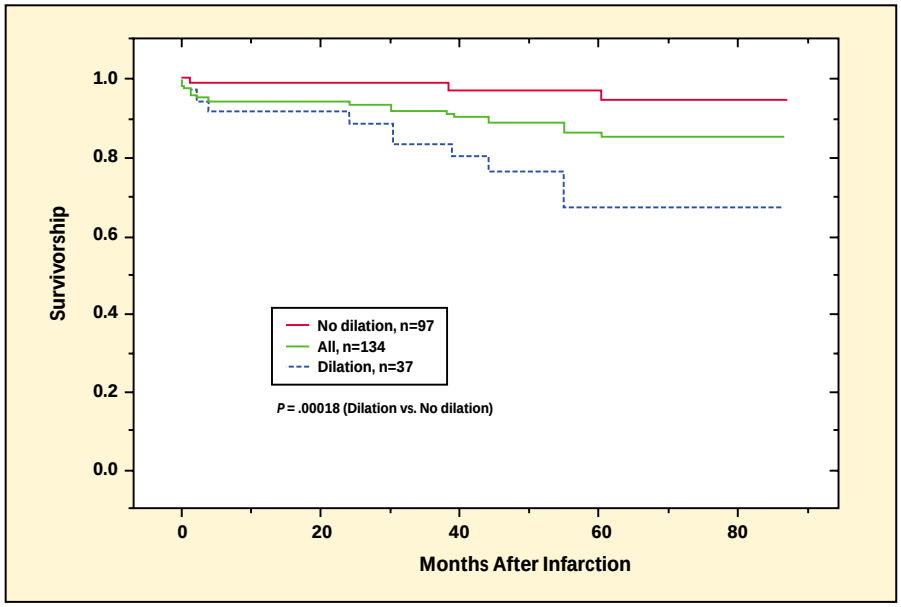
Figure 2. *Comparison of changes in left ventricular (LV) area (as a marker of remodeling) at end systole and end diastole during a 1-year period following myocardial infarction in patients with baseline LV dysfunction from the SAVE trial (y-axis) between those who sustained versus those who did not sustain adverse cardiovascular (CV) events. Regardless of the presence or absence of the angiotensin-converting enzyme inhibitor captopril, patients suffering events had significantly greater increase in areas (ie, more adverse remodeling) compared with those who had no events. Adapted with permission from St. John Sutton et al for the SAVE investigators.*[23]

group of patients from the SAVE trial who were followed for a longer period of time, analysis of cross-sectional area changes over time was performed by echocardiography in an analysis published by St. John Sutton and colleagues.[23] The changes in LV area at 1 year following randomization were significantly related to the long-term follow-up outcome events. Patients who sustained mortal or morbid cardiovascular events had a substantially larger change in LV area (ie, more extensive remodeling) at 1 year after randomization compared with those who did not have cardiovascular events (Figure 2). Of interest and great importance, this finding was independent of the effect of captopril on that same LV area change at 1 year following randomization. In other words, patients on placebo or captopril who had substantial LV remodeling were at significantly higher risk for cardiac events than were those patients on captopril or placebo who did not remodel as extensively. These data provide compelling evidence that the remodeling process itself, independent of drug effect, is associated with adverse natural history outcomes in patients with LV dysfunction. Similar findings have been reported by Gaudron and colleagues[24] in a series of patients studied sequentially after MI, using radionuclide techniques of LV volume determination. Those patients with more substantial post-MI LV dilation were at higher risk of death during follow-up (Figure 3).

Drug Effects on LV Remodeling and Natural History Outcome in Human Heart Failure

Ideally, in a large, randomized, placebo-controlled, long-term follow-up trial of a new therapy for heart failure, all patients would undergo serial analysis of ventricular volume and function at the beginning of the trial and at several time points throughout the course of follow-up. However, even the evaluation of ejection fraction alone, without the more laborious measurements of LV

Figure 3. *Survival curves of post–myocardial infarction (MI) patients who developed left ventricular dilation (dotted blue line) compared with those who did not demonstrate significant remodeling (red solid line). The occurrence of remodeling was associated with a very unfavorable natural history post-MI. Reproduced with permission from Gaudron et al.*[24]



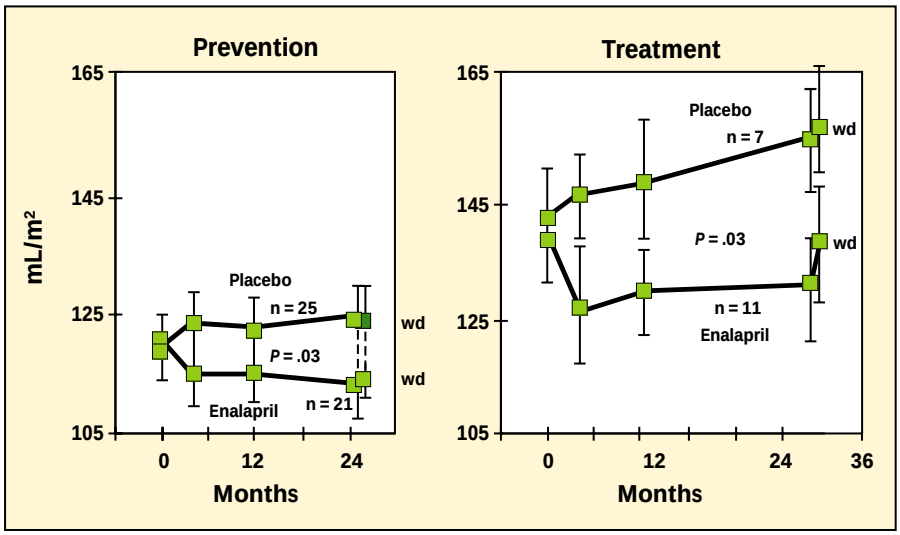
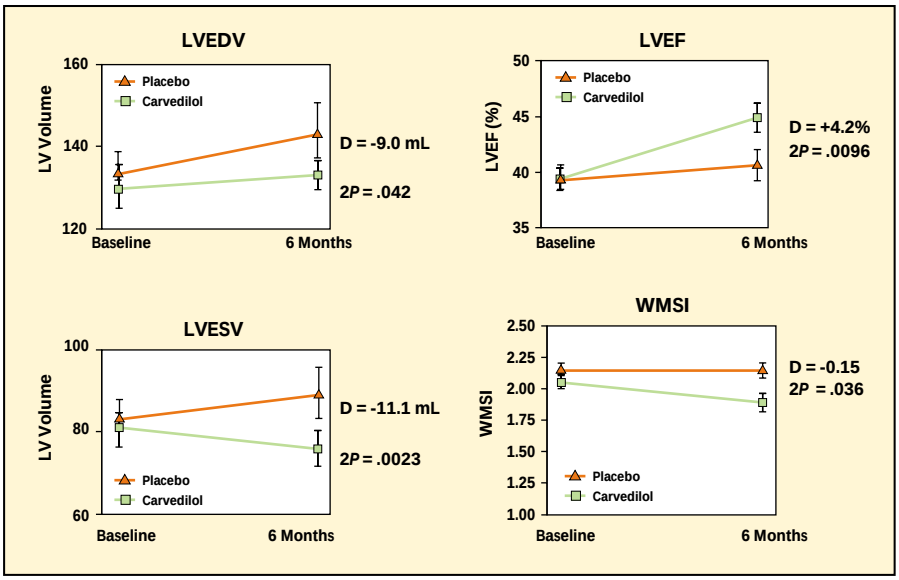


Figure 4. *Changes in left ventricular end-diastolic volume (LVEDV) in mL/m² (y-axis) over time (x-axis) in asymptomatic patients (prevention) as well as symptomatic heart failure patients with left ventricular dysfunction (treatment) from the SOLVD trials while on placebo or enalapril. During long-term follow-up, patients on placebo demonstrate evidence of progressive increase in LVEDV (remodeling), which is prevented by the angiotensin-converting enzyme inhibitor enalapril. wd, restudy approximately 2 weeks after withdrawal of placebo or enalapril. (Adapted from Konstam et al.[26,27])*

volumes, is associated with the addition of significant expense and complexity to such trials, which often involve several thousand patients. Thus, a strategy has emerged over time of studying mechanistic aspects of drug effects on LV function and/or volumes using a substudy model. In this model, more intensive investigation is undertaken in a modest-sized subset of patients within the larger parent trial, with the assumption that the observed results in the substudy are reflective of what might occur if all patients within the trial could be studied; therefore, those results could also be reflective of similar patients not involved in the trial.[25] Although there are some conceptual limitations to this approach, it is practical and has resulted in important insights over the past decade.

One of the first trials to use this method to examine drug effects on LV volumes and function was the Studies of Left Ventricular Dysfunction (SOLVD) trial. In this study, patients with mild-to-moderate clinical heart failure and evidence of LV systolic dysfunction (LVEF ≤35%) were randomized in a double-blind fashion to long-term follow-up on either enalapril at a target dose of 10 mg, bid, or to placebo.[25] A radionuclide ventriculographic substudy examined serial changes in LV volumes and function among patients at selected centers in the SOLVD Treatment Trial (those with symptomatic heart failure) as well as in the SOLVD Prevention Trial (those with asymptomatic LV dysfunction). The results provided information for the first time on long-term changes in LV volume in the heart failure setting, as well as providing information on the long-term effect of an ACE inhibitor on that process.[26] Among the group of symptomatic heart failure patients randomized to placebo, there was a steady increase in LV volumes (both end-diastolic and end-systolic) over approximately 3 years of follow-up, clear evidence of LV remodeling (Figure 4). Also of importance is that these findings were observed remote from initial MI among those with ischemic cardiomyopathy, as the average time from infarction to ran-

Figure 5. *Effect of ß-blockade with carvedilol on measures of post–myocardial infarction remodeling in the contemporary treatment era from the CAPRICORN trial. Favorable changes compared with placebo were seen in left ventricular (LV) end-diastolic volumes (LVEDV), end-systolic volumes (LVESV), ejection fraction (LVEF), and wall motion score index (WMSI). D, change. Adapted from Doughty et al.[29]*



domization among patients with ischemic cardiomyopathy was approximately 8 months. Moreover, these data provided the first evidence that ACE inhibitors favorably affected the remodeling process.[26] Among patients randomized to enalapril, there was a relatively early reduction in LV volumes (first observed at the 3-month post-randomization time point), which was maintained out to an average of 33 months during the last observation while patients were on the study drug. Two weeks after withdrawal of the study drug, volume studies were repeated to examine what the long-term natural history effect of the ACE inhibitor was in the absence of an acute dose-by-dose unloading effect. Compared with the final "on-drug" time point 2 weeks earlier, the subsequent withdrawal volumes in the enalapril group increased somewhat, back toward the initial baseline that had been observed approximately 3 years earlier. However, LV volumes were still significantly lower than those in patients on placebo, providing evidence that the ACE inhibitor enalapril favorably affected the structural alterations of LV remodeling compared with patients on placebo. In the parent trial, the ACE inhibitor enalapril was associated with a significant reduction in mortality. Thus, although the volume changes were observed in only a relatively small subset of patients, it is reasonable to conclude that the effect of enalapril on the remodeling process was in part associated with or responsible for the observed favorable effect on mortality. In a subsequent report, patients from the SOLVD Prevention Trial (ie, those with asymptomatic LV dysfunction) were also shown to display evidence of remodeling over time while on placebo, though over a more prolonged period of time when compared with the symptomatic group of patients.[27] This unfavorable progressive increase in LV volume was attenuated by treatment with enalapril.

A strategy has emerged over time of studying mechanistic aspects of drug effects on LV function and/or volumes using a substudy model.

ß-blockers have also been examined for their effect on post-MI LV remodeling. Basu and colleagues[28] administered intravenous followed by oral carvedilol to a broad population of post-MI patients in a placebo-controlled study. These investigators reported favorable effects on post-MI clinical events. In a subpopulation of those with LVEF <45%, post-MI treatment with carvedilol was associated with favorable inhibition of the remodeling process, which was further associated with a reduction in adverse clinical outcomes. Application of these data to contemporary practice are somewhat limited by the absence of background ACE inhibitor therapy in the population.

More relevant to contemporary practice are the preliminary data from the Carvedilol Postinfarction Survival Control in Left Ventricular Dysfunction (CAPRICORN) trial examining the incremental effect of ß-blockade (with carvedilol) in the post-MI setting over and above the effects of other established therapies, including ACE inhibitors.[29] Over a 6-month treatment period post-MI, the group treated with carvedilol had significantly favorable effects on LV end-diastolic volumes, LV end-systolic volumes, LV ejection fraction, and wall motion score index (Figure 5). Thus, in the current era, ß-blockade appears to add favorable and independent effects on the post-MI remodeling process in the presence of ACE inhibition. The effects on the remodeling process in this trial were accompanied by favorable effects on natural history outcomes.[30]

The mechanism whereby ß-blockers attenuate remodeling in the post-MI setting has not been extensively studied in experimental preparations. In one such study, Wei and coworkers[31] found that in a rat model of post-MI remodeling, carvedilol has a greater impact on reduction in noninfarct zone collagen deposition compared with metoprolol, at doses producing equivalent ß-blocking effects on heart rate (Figure 6).

The effects of longer-term post-MI ß-blockade have also been reported. The Australia-New Zealand investigators[32] studied patients with chronic LV dysfunction late after MI who already had been treated with optimal doses of ACE inhibitors. The subjects were randomized in a double-blind fashion to treatment with carvedilol or to placebo. Over 12 months, patients randomized to placebo had a substantial increase in LV volume, whereas those randomized to carvedilol had a reduction in LV volume observed both 6 and

Over 12 months, patients randomized to placebo had a substantial increase in LV volume, whereas those randomized to carvedilol had a reduction in LV volume observed both 6 and 12 months after randomization.

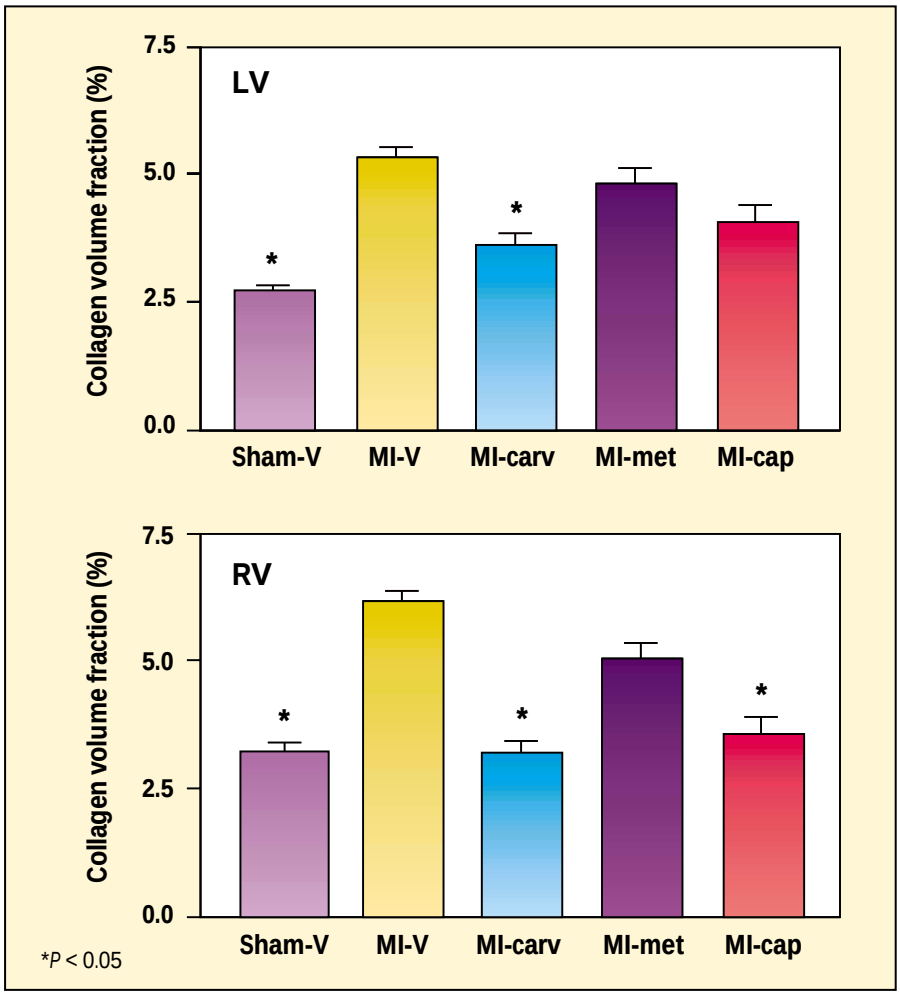


Figure 6. *Measures of collagen volume fraction in the left ventricle (LV; top panel) and right ventricle (RV; bottom panel) of rats post–myocardial infarction (MI). Data are from Sham-operated (Sham) and post-MI (MI) models treated with vehicle (V), carvedilol (carv), metoprolol (met), or captopril (cap). Reproduced with permission from Wei et al.*[31]

12 months after randomization. It is important to note that these findings were observed in patients who were already treated with ACE inhibitors. Again, analogous to the findings seen in the SOLVD trial, mortality was reduced in larger studies of carvedilol,[33,34] suggesting that the favorable effects on LV volumes play an important role in the observed reduction in mortality. Similar findings on the remodeling process have been reported following the use of long-acting metoprolol in patients with chronic LV dysfunction.[35]

Not all published studies have reported favorable effects of drug intervention on the remodeling process. In a relatively small study of the dopaminergic receptor antagonist ibopamine, radionuclide ventriculographic studies only 1 month after randomization to ibopamine or placebo demonstrated an increase in both end-diastolic and end-systolic volume indexes compared with placebo.[36] Subsequent studies demonstrated an unfavorable effect on natural history outcomes of ibopamine in heart failure patients.[37]

These studies all suggest the possibility that the effect of a drug therapy on LV remodeling may be substantially associated with the drug's effect on natural history outcomes and that it may be reasonable to consider the remodeling effect as a surrogate for the natural history outcome effect. This concept is supported by a meta-analysis of all randomized clinical trials prior to 1999 examining drug effects on LV volumes and/or ejection fraction changes.[38] The analysis suggested that drugs associated with a favorable effect on natural history in general had a more pronounced effect on reduction in LV volumes in the short-term studies compared with drugs with either neutral or unfavorable effects. The effect of drug therapy on LV volumes seemed to have a closer association to the natural history outcome effect than changes in ejection fraction.

What is the link between the remodeling process, or its attenuation, and the clinical events characteristic of long-term follow-up in post-MI patients with LV dysfunction? Outcome events may manifest as progressive heart failure, an event that is likely to be very powerfully related to the remodeling process or potentially to sudden arrhythmic cardiac death. The latter likely results from a milieu that is enhanced by the structural and cellular changes associated with the remodeling process. Recent data from St. John Sutton and coworkers[39] suggest that the magnitude of remodeling is related to markers of ventricular arrhythmia risk. Similar data have been reported by Gaudron and colleagues.[24] These investigators found that the magnitude of post-MI LV remodeling correlated with several measures of electrical instability, such as QTc prolongation and Lown arrhythmia score on Holter monitoring. However, other factors that

affect the natural history of heart failure and LV dysfunction post-MI likely have less association with the remodeling process, such as recurrent acute myocardial infarction, pathologic evidence of which has been found in autopsy studies underlying a substantial number of deaths in a large heart failure trial.[40]

The addition of ß-blockade post-MI appears to add independently favorable effects to those of ACE inhibition on the remodeling process, further improving the natural history of patients with post-MI LV dysfunction.

Some therapies that have a favorable effect on the remodeling process do not ultimately demonstrate overall favorable clinical effects. As an example, the cytokine inhibitor etanercept has been shown to have a dose-dependent effect on reversal of the remodeling process (ie, reduction in LV end-diastolic volumes) over 3 months of therapy.[41] Larger, longer-term clinical trials have been stopped prematurely, however, suggesting lack of a long-term favorable effect.

Conclusion

Studies such as those cited above suggest that the post-MI remodeling process is related to and associated with the later, long-term progression of LV dysfunction, heart failure symptoms, and mortality. Drug therapies that slow or reverse the remodeling process also appear to have favorable natural history effects in the short term as well as during long-term

Main Points

- Left ventricular (LV) remodeling is related to clinical outcomes that represent the natural history of the heart failure syndrome, such as mortality, and therapeutic interventions in humans that slow or reverse the process of LV remodeling, such as angiotensin-converting enzyme (ACE) inhibitors and ß-blockers, appear to have a favorable effect on that natural history.
- Experimental data support the premise that the renin-angiotensin-aldosterone system (RAAS) plays a central role in the pathophysiology of ventricular remodeling and heart failure progression. In addition, these data also support a pivotal role for the RAAS in the pathophysiology of post–myocardial infarction (MI) progressive LV remodeling and underscore the importance of pharmacologic inhibition of the renin-angiotensin hormonal axis.
- In the post-MI setting, a measurement of ejection fraction or end-systolic volume at one point in time in a population provides information regarding potential natural history outcomes; patients with lower ejection fraction and particularly larger ventricular volumes have substantially higher risk of death as well as the onset of symptomatic heart failure during follow-up.
- The Survival and Ventricular Enlargement (SAVE) trial examined the effect of captopril on clinical outcomes in post-MI patients with LV ejection fraction ≤40%. Such patients were randomized to captopril at a target dose of 50 mg, tid, or to placebo, and the results confirmed those reported in the initial post-MI rat model studies, demonstrating a significant reduction in morbidity and mortality among patients randomized to receive captopril.
- Patients who sustained mortal or morbid cardiovascular events had a substantially larger change in LV area at 1 year after randomization (ie, more extensive remodeling) compared with those who did not have cardiovascular events. Of interest and great importance, this finding was independent of the effect of captopril on that same LV area change at 1 year following randomization.
- The results of the Studies of Left Ventricular Dysfunction (SOLVD) trial provided information for the first time on long-term changes in LV volume in the heart failure setting, as well as providing information on the long-term effect of an ACE inhibitor on that process. Moreover, these data provided the first evidence that ACE inhibitors favorably affected the remodeling process.
- More relevant to contemporary practice are the preliminary data from the Carvedilol Postinfarction Survival Control in Left Ventricular Dysfunction (CAPRICORN) trial examining the incremental effect of ß-blockade (with carvedilol) in the post-MI setting over and above the effects of other established therapies, including ACE inhibitors. Over a 6-month treatment period post-MI, the group treated with carvedilol had significantly favorable effects on LV end-diastolic volumes, LV end-systolic volumes, ejection fraction, and wall motion score index.
- The effect of a drug therapy on LV remodeling may be substantially associated with the drug's effect on natural history outcomes, and it may be reasonable to consider the remodeling effect as a surrogate for the natural history outcome effect.

therapy. In the post-MI setting, substantial evidence suggests that ACE inhibition attenuates the remodeling process associated with favorable clinical effects. Moreover, the addition of ß-blockade post-MI appears to add independently favorable effects to those of ACE inhibition on the remodeling process, further improving the natural history of patients with post-MI LV dysfunction. ■

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