Research Advances Series

Ventricular Remodeling After Myocardial Infarction
Experimental Observations and Clinical Implications

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An acute myocardial infarction, particularly one that is large and transmural, can produce alterations in the topography of both the infarcted and noninfarcted regions of the ventricle. This remodeling can importantly affect the function of the ventricle and the prognosis for survival. In the early period, infarct expansion has been recognized by echocardiography as a lengthening of the noncontractile region. The noninfarcted region also undergoes an important lengthening that is consistent with a secondary volume-overload hypertrophy and that can be progressive. The extent of ventricular enlargement after infarction is related to the magnitude of the initial damage to the myocardium and, although an increase in cavity size tends to restore stroke volume despite a persistently depressed ejection fraction, ventricular dilation has been associated with a reduction in survival. The process of ventricular enlargement can be influenced by three interdependent factors, that is, infarct size, infarct healing, and ventricular wall stresses. A most effective way to prevent or minimize the increase in ventricular size after infarction and the consequent adverse effect on prognosis is to limit the initial insult. Acute reperfusion therapy has been consistently shown to result in a reduction in ventricular volume. The reestablishment of blood flow to the infarcted region, even beyond the time frame for myocyte salvage, has beneficial effects in attenuating ventricular enlargement. The process of scarification can be interfered with during the acute infarct period by the administration of glucocorticosteroids and nonsteroidal antiinflammatory agents, which result in thinner infarcts and greater degrees of infarct expansion. Modification of distending or deforming forces can importantly influence ventricular enlargement. Even short-term augmentations in afterload have deleterious long-term effects on ventricular topography. Conversely, judicious use of nitroglycerin seems to be associated with an attenuation of infarct expansion and long-term improvement in clinical outcome. Long-term therapy with an angiotensin converting enzyme inhibitor can favorably alter the loading conditions on the left ventricle and reduce progressive ventricular enlargement as demonstrated in both experimental and clinical studies. With the former therapy, this attenuation of ventricular enlargement was associated with a prolongation in survival. The long-term clinical consequences of long-term angiotensin converting enzyme inhibitor therapy after myocardial infarction is currently being evaluated. Although studies directed at attenuating left ventricular remodeling after infarction are in the early stages, it does seem that this will be an important area in which future research might improve long-term outcome after infarction. (Circulation 1990;81:1161–1172)

Tennant and Wiggers' classic description of regional wall motion changes after acute coronary artery ligation describes "local enfeeblement of contraction" as well as "systolic expansion." These observations of local contractile dysfunction were recognized to be the result of acute ischemia and led to an understanding of the pathophysiology in acute myocardial infarction. During the past 12 years, it has become increasingly appreciated that myocardial infarcts, particularly large transmural infarcts, result in complex alterations in ventricular architecture involving both the infarcted and noninfarcted zones. These alterations, often referred to as "ventricular remodeling," can profoundly affect the function of the ventricle and, thereby, the patient's prognosis. Recently, interest has developed in limiting ventricular remodeling, with the objective of improving ventricular function and clinical outcome. The changes in

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ventricular architecture consequent to acute myocardial infarction and efforts to pharmacologically alter these changes are the subject of this article.

Infarct Expansion

Infarct expansion has been a cornerstone in our understanding of the changes in ventricular architecture occurring as a consequence of acute myocardial infarction. During the first hours after myocyte necrosis, edema and inflammation are localized to the infarcted region. This is followed by a long-term phase of fibroblast proliferation and collagen deposition, that is, scar formation. Depending on the species, this entire process is completed within weeks to months. Before and during the period of resorption of necrotic tissue but before there is extensive deposition of collagen and an increase in the tensile strength, the infarcted region can thin and elongate. This process, which was described in 1978 by Hutchins and Bulkley, has been termed “infarct expansion” and defined as “acute dilatation and thinning of the area of infarction not explained by additional myocardial necrosis.” Histological examination has revealed that this thinning of the infarcted region is a consequence of slippage between muscle bundles, resulting in a reduction in the number of myocytes across the infarcted region. During the course of healing, connective tissue cells enter the myocyte compartment and connect disrupted myocyte fibers, providing resistance to further stretching.

In patients, infarct expansion can be recognized by echocardiographic evidence of distortion of ventricular topography as a consequence of elongation of the noncontractile region, which is not associated with reerelevation of serum enzyme, evidencing further myocardial necrosis. Operationally, short-axis two-dimensional echocardiography at the papillary muscle level is used to determine anterior and posterior segment lengths. Expansion is considered to be present when the akinetic or dyskinetic segment exceeds the upper limit of normal for control subjects. (Figure 1).

Infarct expansion does not occur uniformly after all infarcts but it is observed most frequently in large transmural infarctions. Patients exhibiting infarct expansion are more likely to experience complications such as the development of congestive heart failure, aneurysm formation, and myocardial rupture. The latter can be viewed as an early extreme form of infarct expansion in which the expanded region is so thin that it is not capable of maintaining the integrity of the ventricular wall before the deposition of collagen and scar formation. Distortion of the ventricular contour leading to aneurysm formation is a common occurrence in patients with infarct expansion and contributes to the increase in mortality and morbidity of these patients. Patients developing an aneurysm early in the course of anterior infarction have a much higher 1-year mortality rate than anterior infarct patients with comparably reduced ejection fraction but more preserved ventricular contour.

Infarct expansion seems to be more common in patients experiencing transmural infarctions involving the anterior-apical surface than other regions of the left ventricle. The anterior-apical region is a particularly vulnerable segment of the ventricle for expansion because it is the thinnest and has the greatest curvature. Therefore, any expansion and thinning and the attendant decrease in curvature would result in a relatively greater augmentation of deforming forces at the apex than other regions of the ventricle.

In addition to expansion, myocardial infarction causes a number of other changes in the ventricle. Applying ultrasonic crystals across three regions of the left ventricle of dogs, Theroux et al characterized the sequential alterations in myocardial function in the infarcted and noninfarcted regions during a 3-week period after permanent coronary artery ligation. They demonstrated that the initial dyskinesis in
the infarct zone often improved to akinesis, which was then sustained during the subsequent period of observation. Of particular interest were their observations of the segment length and contractile pattern of the uninfarcted zone, remote from the coronary occlusion. A progressive increase in the end-diastolic length, which was coupled with greater relative shortening, was observed in this region. These changes in the uninvolved region were likened to the compensatory responses observed in a long-term volume-overload model of eccentric hypertrophy of the left ventricle. Therefore, myocardial infarction induced a primary alteration in function of the infarcted region as well as time-dependent secondary changes in the noninfarcted tissue. Erlebacher et al., demonstrated that patients with infarct expansion also had evidence of dilation of the noninfarcted region on follow-up evaluations. McKay et al. demonstrated with serial contrast ventriculograms that ventricular enlargement was present by 2 weeks after Q wave myocardial infarction. This global ventricular enlargement could not be explained by acute distention because left ventricular filling pressure was actually lower at the 2-week study than during the acute infarct period. Serial echocardiographic studies indicated that this remodeling involved both the infarcted as well as noninfarcted regions of the left ventricle. The magnitude of total left ventricular cavity enlargement 2 weeks after infarction correlated directly with the extent of the akinesis and dyskinesis present on the acute ventriculogram.

In the rat model of myocardial infarction, we observed that both ventricular function and survival are related to the size of the myocardial infarction. In this experimental model, ventricular volume could be compared at a common distending pressure, and in the long-term infarcted myocardium, left ventricular volume was found to be a function both of the extent of histological damage and the time after infarction (Figure 2). Progressive enlargement of the infarcted ventricle at a common distending pressure occurred as a consequence of ventricular remodeling with a shift of the pressure-volume relation to the right, that is, along the volume axis. Much of this increase in volume was apparent at low filling pressures, indicating a change in the capacitance of the minimally distended chamber. Another interesting finding in these animal studies was that cavity enlargement continued long after complete healing of the infarction. Thus, after the experimental myocardial infarction, left ventricular volume increased progressively as a time-dependent process that was related to the extent of histological damage. Although the infarct region is histologically healed and pronounced ventricular enlargement is already present by 3 weeks, an additional 30% augmentation in ventricular volume was observed in animals studied 3 months after moderately sized (20–40% of the left ventricle) infarctions. This observation indicates that, in addition to any changes in the infarct, progressive changes in the noninfarcted regions of the left ventricle contribute to the overall process of chamber enlargement.

Clinically, it is well recognized that survivors of myocardial infarctions can demonstrate pronounced cavity enlargement that is not explained by an elevated filling pressure, suggesting that, similar to the experimental model of infarction and of eccentric hypertrophy secondary to volume overload, a shift to the right of the ventricular pressure-volume curve occurs. Linzbach has shown that the length of the sarcomere from pathologically enlarged hearts is normal, indicating that the volume increase of the impaired ventricle is a consequence of a rearrangement of the myofibrils across the wall rather than a simple stretching of sarcomeres. It is only relatively recently, however, that the progressive nature of this enlargement, beyond the early convalescent period of the infarct, has been appreciated. In many instances, early infarct expansion is associated not only with immediate but also with continued (late) cavity enlargement. In evaluating the overall response of ventricular volume to infarction, both the early and late alterations in the infarcted and noninfarcted regions must be considered. Although the predominant early changes occur in the thinning and lengthening of the infarct, dilation and eccentric hypertrophy of the viable region also commence early, and this process can continue long after healing of the infarct.

**Ventricular Dilation as an Adaptive Process**

Ventricular dilation after myocardial infarction can be viewed as a response to dysfunction, and in many respects, its extent reflects the magnitude of the primary damage induced by the infarction. Thus, global contractile performance as assessed by ejection fraction declines in direct relation to the extent of the histological damage. In patients with acute
myocardial infarction, the reduction in ejection fraction has been related to serial serum creatinine phosphokinase estimates of infarct size.\textsuperscript{31} In our animal studies of healed infarction where infarct size is histologically determined as the percentage of the left ventricular surface that is fibrous tissue, ejection fraction declines in direct relation to infarct size (Figure 3). Although mathematical models correctly predict this acute reduction in ejection fraction in proportion to the extent of noncontractile myocardium,\textsuperscript{32,33} stroke volume unlike ejection fraction does not consistently decline after infarction.\textsuperscript{18,24,25} Both acute and long-term compensatory responses serve to maintain the stroke volume as ejection fraction declines. Acute distension of the viable myocardium and the operation of the Frank-Starling mechanism, as well as augmentation of chronotropic and inotropic activity through adrenergic receptor stimulation, tends to maintain pump function with the abrupt loss of contractile tissue. These acute compensatory mechanisms, however, are inadequate to maintain stroke volume when the noncontractile region involves more than approximately 20\% of the left ventricular circumference.\textsuperscript{34} Augmenting cavity size by long-term dilation, however, can restore stroke volume despite a persistently depressed ejection fraction.\textsuperscript{35} Through the operation of Laplace’s law, however, this dilation would augment diastolic and systolic wall stress and thereby stimulate further ventricular enlargement.\textsuperscript{36} When the cumulative loss of myocardium is large, a vicious cycle can be created in which the dilation initiated to maintain pump function continues, that is, “dilatation begets more dilatation.”\textsuperscript{26,34,35,37} As a result of the increased cavity volume and the relative lack of change in ventricular radius during ejection, the wall stress of the impaired ventricle can fail to decline normally during ejection.\textsuperscript{34,38}

This augmentation in wall stress of the dilated ventricle can then serve as a stimulus for additional myocyte hypertrophy, which can offset the increased wall stress and reduce the stimulus for further enlargement. Anversa and coworkers\textsuperscript{39} have measured the growth of the viable myocardium after experimental coronary artery ligation and confirmed that myocyte hypertrophy with up to 78\% increases in mean cell volume occurs after large infarctions.\textsuperscript{39} They demonstrated, however, that this cellular hypertrophy was inadequate to fully compensate for the degree of myocyte loss.\textsuperscript{39} Although ventricular hypertrophy can restore wall stress after myocardial infarction, with severe insults the extent of cavity dilation (volume) is often out of proportion to the augmentation in mass.\textsuperscript{20,21,40} Summarily, ventricular enlargement after infarction can be viewed as an initial compensation to maintain stroke volume after the loss of contractile tissue; however, a precarious balance can be exceeded in which increased cavity volume with insufficient compensatory hypertrophy results in loading conditions promoting further enlargement and dysfunction.

### Ventricular Enlargement and Prognosis

Roentgenographic evidence of cardiac enlargement after a myocardial infarction is an ominous finding that is associated with distinctly reduced survival.\textsuperscript{41,42} Using calibrated chest roentgenograms to determine left heart dimension, Kostuk and co-investigators\textsuperscript{41} reported a threefold increase in mortality (24\% vs. 8\%) for survivors of myocardial infarction developing left heart enlargement as compared with those maintaining a normal silhouette. Moreover, in almost 1 year of follow-up, 32\% of the patients with enlarged heart and only 2\% of the patients with normal-size heart manifested New York Heart Association class III symptoms of either congestive heart failure or angina. Roentgenography, however, is a relatively insensitive means of detecting ventricular enlargement. The application of quantitative left ventriculography has provided evidence that the augmentation, in the relative risk of death, increases in direct relation to the magnitude of the ventricular enlargement.\textsuperscript{43,44} It has been observed
that increases in cineangiographic left ventricular volume is predictive of a poor prognosis, even in the presence of normal overall heart size on plain chest roentgenography. \(^{43,44}\) White et al.\(^ {43}\) found that, although survival after myocardial infarction correlated inversely with left ventricular end-diastolic and end-systolic volumes as well as correlated directly with ejection fraction, the most powerful predictor of death was end-systolic volume; progressive increments of only 25 ml in end-systolic volume, which is well below detection on chest roentgenography, increased the relative risk of death in an exponential manner.\(^ {43}\) Survivors of myocardial infarction with left ventricular end-systolic volumes of 75 and 125 ml had a relative risk of death of approximately 2.5-fold and fivefold, respectively, over that of patients with normal (30–55 ml) end-systolic volumes. Indeed, multivariate analysis revealed that the angiographic left ventricular volume was the most powerful predictor of reduced survival, that is, more powerful than the extent of coronary artery disease.\(^ {43,44}\)

The importance of this association between ventricular enlargement and reduced survival has been strongly supported by experimental studies that have demonstrated that the process of enlargement can be modified by long-term pharmacological therapy. We postulated that therapy to reduce the force distending the myocardium might reduce the extent of ventricular enlargement and improve the survival rate.\(^ {19,22,37}\) In the rat model of infarction, long-term captopril therapy was shown to alter the diastolic pressure-volume relation of the left ventricle (reducing ventricular volume at any level of distending pressure), resulting in smaller ventricular volumes in treated animals despite comparable degrees of histological damage.\(^ {22}\) In a separate series of studies in the same experimental model, these favorable morphological changes were shown to be associated with an improvement in survival.\(^ {19}\) Thus, therapy with an angiotensin converting enzyme (ACE) inhibitor initiated long after infarct size could be modified (2 or 14 days after infarction) altered both the compliance and volume of the ventricle and resulted in an improvement in long-term survival rate. The greatest benefit in survival rate was observed in animals with moderate-size infarcts comprising 20–40% of the left ventricle, that is, the group that also exhibited the maximum attenuation in volume enlargement.\(^ {19,22,37}\)

**Modification of Ventricular Enlargement**

The process of ventricular enlargement after infarction can be influenced by three interdependent factors, that is, modification of 1) infarct size, 2) infarct healing, and 3) ventricular wall stress. The extent of damage of the ventricle, as assessed by the fraction of the circumference exhibiting akinesis and dyskinesis, as well as the transmurality of the acute infarction are crucial determinants of the magnitude of ventricular enlargement. Clearly, the most effective way to prevent or minimize secondary ventricular enlargement after infarction is to limit the extent of the initial insult. Patients surviving an infarct with minimal regional wall motion abnormalities do not exhibit measurable changes in ventricular size or shape. Although ventricular enlargement can be observed after inferior as well as anterior infarcts, anterior wall infarctions are associated with greater ventricular enlargement\(^ {17,45,46}\) and a higher late mortality.\(^ {47}\)

Myocardial reperfusion performed during the period in which salvage of myocardium is possible has been shown to result in a reduction in infarct size with associated improvements in regional and, in many instances, in global ventricular performance.\(^ {46,48–52}\) Two important studies evaluated left ventricular volumes by quantitative ventriculography in the weeks after infarction, and both demonstrated that patients receiving thrombolytic therapy had a smaller ventricular volume than comparable patients with acute infarcts not receiving this therapy.\(^ {46,50}\) A recent evaluation of a cohort of the GISSI trial followed by echocardiographic assessments of ventricular volumes indicates that thrombolytic therapy was associated with reduced ventricular volume both before discharge and 6 months after myocardial infarction.\(^ {53}\)

The prolongation of survival in patients treated with acute reperfusion therapy was initially attributed to a salvaging of myocytes and reduction of impairment of ventricular function. The 18–47% reductions in mortality observed in the large randomized trials of thrombolytic therapy, however, seemed disproportionately large with regard to the modest improvements in ejection fraction that have been associated with the use of thrombolytic therapy.\(^ {54,55}\) This relative disparity between the degree of improvement in long-term survival and global left ventricular function suggests that reperfusion therapy offers benefits in addition to those associated with actual salvage of myocardium.\(^ {54,55}\)

By salvaging a rim of epicardium and thereby reducing the fraction of the infarct that is transmural,\(^ {56}\) early reperfusion would be anticipated to reduce infarct expansion. Touchstone et al.\(^ {57}\) demonstrated that acute infarct patients with infarct expansion despite thrombolytic therapy were likely to have an occluded infarct-related artery. Therefore, reestablishment of flow was required to observe this beneficial effect of thrombolytic therapy.\(^ {57}\) Even late coronary artery reperfusion at a time after any possible myocardial salvage, however, has also been shown in animal experiments to reduce the lengthening and thinning of the infarcted region.\(^ {58–60}\) In the rat, Hochman and Choo\(^ {58}\) showed that reperfusion 2 hours after coronary ligation limited the extent of expansion without influencing infarct size or the transmurality of the infarction. A possible explanation is that the late restoration of flow to the already infarcted zone promotes scar healing that prevents or reduces the expansion process. In one study, collagen content and tensile strength of late reperfused scars measured 3 weeks after infarction were found to be
The relative tensile strength of the late reperfused region during the first few days after infarction, that is, when infarct expansion occurs, however, is an important unresolved question. Late reperfusion has been shown by echocardiography to improve function in the infarct region. It can do so both by limiting expansion as well as by supporting contractile function of the remaining viable myocytes within the infarcted region.

Establishing patency of the infarct-related artery also seems to exert a beneficial effect by reducing aneurysm formation. In a series of 47 consecutive patients suffering a first anterior infarct, Hirai and coworkers found that left ventricular aneurysm was much less likely to develop in patients with successful reperfusion or collateral flow to the infarct zone. Similarly, Jeremy et al have shown that the development of late ventricular enlargement after infarction is more likely to occur in survivors with a total occlusion of the infarct-related vessel.

In a study of ventricular enlargement after anterior infarction in which the baseline assessment of ventricular size was conducted 3 weeks after infarction, we found that total occlusion of the infarct-related vessel was an important predictor of further ventricular enlargement at 1 year (Figure 4). This increase in volume could not be explained by greater distension because the filling pressures did not differ between the groups or during time. These late effects of infarct artery patency on ventricular size seem to be related to effects on the noninfarcted region because this late phase of enlargement is not a consequence of further infarct expansion. In the infarcted ventricle, the greatest regional wall stress and myocyte hypertrophy is at the border between the infarcted and viable myocardium. It is possible that patency of the infarct-related vessel supports the function of this particularly vulnerable area of myocardium and thereby limits further distortion. Electrical stability can be another important long-term benefit imparted by maintaining a patent vessel supplying the infarcted region.

This recent information, that the patency of the infarct-related vessel seems to have not only important early influences on the extent of necrosis and on expansion of the infarct zone but also late effects on global ventricular size and electrical stability, supports the observations of improved long-term survival rate in patients with patent versus occluded infarct-related vessels. In survivors of acute myocardial infarction with angiographic disease limited to only one coronary artery, patients with no or minimal anterograde perfusion of the infarct artery had a much higher risk of experiencing unstable angina, congestive heart failure, or death during long-term follow-up. In this important, albeit retrospective analysis, these pronounced differences in morbid and fatal events could not be explained by baseline clinical assessment or measures of left ventricular function.

**Infarct Healing**

Infarct expansion occurs within hours after infarction before extensive fibroblast proliferation and collagen deposition, both of which result in a firm scar, have taken place. During this early period, the infarcted region is particularly vulnerable to distorting forces. Once healed, the scar itself is relatively nondistensible and much more resistant to further deformation. As discussed above, both early and late reperfusion favorably limit the deformation of the infarct region during scar formation. In addition to reperfusion, pharmacological therapy with antiinflammatory agents can affect the healing process, and thereby exert an influence on the topographic alterations of the ventricle.

A consistent finding in experimental infarct models is that the administration both of glucocorticosteroids and nonsteroidal antiinflammatory agents during the acute phase of the infarct results in a thinner scar region that is associated with more infarct expansion. The actual collagen content of the healed infarct in animals receiving antiinflammatory therapy seems to be similar to that of scar tissue of nontreated animals. The antiinflammatory agents, therefore, can be slowing the time course of healing and allowing ventricular wall tension to act on deformable myocardium for a longer time, rather than altering the ultimate composition of the infarct. The detrimental effect of antiinflammatory agents on ventricular topography can result from their prolongation of the period during which the infarct is extensible and under the influence of deforming forces.

The clinical importance of these experimental findings has been emphasized in a recent study by
Jugdutt and Basualto. Patients receiving either ibuprofen or indomethacin during the early infarction period demonstrated greater lengthening and thinning of the infarcted region than similar patients not receiving these antiinflammatory compounds. These findings of greater infarct segment length and distorsion have important clinical impact because patients treated with indomethacin had a higher prevalence of left ventricular aneurysm formation and symptomatic congestive heart failure during follow-up. Interestingly, although glucocorticosteroids and nonsteroidal antiinflammatory agents have been shown to interfere with myocardial infarct scar formation, aspirin has no such effect. Therefore, aspirin is clearly preferable as an antiinflammatory agent in early infarction.

**Mechanical Forces**

Since the classic description of Tennant and Wiggers, that the interruption of coronary blood flow leads to a local enfeeblement of contraction and systolic bulging, it has been apparent that mechanical forces play an important role in deforming the hypoperfused noncontracting region. Dyskinesis is an important manifestation of this mechanical force that distends the noncontracting myocardium. The elongation and further thinning of the infarcted region that is observed with infarct expansion is an exaggeration of the response to the intracavitary distending forces. Modification of the distending or deforming forces acting on both the necrotic and viable myocardium can be expected to result in both acute and long-term changes in the extent of expansion of the infarct on the overall cavity size of the left ventricle and ultimately on the accompanying hypertrophy.

Experimentally, even transient modest pressure elevation by methoxamine infusion 1–5 hours after coronary artery ligation exacerbated infarct expansion and thinning assessed 1 week after infarction. Despite comparable infarct hydroxyproline content, dogs exposed to the augmented afterload demonstrated more distortion of this region. This study suggests that even relatively brief alterations in the loading conditions during the period of scar formation might have long-term implications on ventricular shape and size. Long-term augmentation in afterload produced by aortic banding 3 weeks before coronary artery ligation in rats increased the extent of left ventricular enlargement and infarct thinning. In a clinical study, Piérard et al demonstrated that infarct expansion was more likely to occur in patients with higher arterial pressure and systemic vascular resistance. It is possible that the earlier observations in patients of a beneficial effect of preventing hypertension during the acute infarct period might be related, in part, to limitation of ventricular deformation.

Exercise represents a nonpharmacological mechanism of transiently augmenting wall stress. Forced swimming of normal and even hypertensive rats causes eccentric ventricular hypertrophy with a proportional increase in both mass and volume. The imposition, even short-term, of this additional hemodynamic burden of swimming after coronary ligation in rats has been shown to cause greater scar thinning. In another study in the rat infarct model, a more moderate exercise program using daily treadmill activity during the first week of experimental infarction did not result in further distortion of the infarct region. Jugdutt et al demonstrated in patients that an exercise program that commenced 15 weeks after infarction and continued for 12 weeks exerted an adverse effect only on survivors of large Q wave anterior myocardial infarctions in whom the percentage of the echocardiographic left ventricular contour that was akinetic or dyskinetic exceeded 18%. In these patients with extensive infarctions, the group that exercised had echocardiographic evidence of deterioration in ventricular function and further distortion of infarct region topography with an increase in the expansion index and thinning ratio (Figure 1) that was not observed in a matched control group. This important study illustrates that the hemodynamic stress of a graded exercise program can lead to a further distortion of left ventricular contour in patients with large Q wave infarctions and extensive wall motion abnormalities. This study raises a cautionary note that although exercise after infarction is generally well tolerated, the potential to alter ventricular topography adversely exists in highly selected patients.

Attention has also been focused on the potential benefits of reducing wall stress even in normotensive patients in an effort to favorably alter left ventricular topography after infarction. Flaherty and coworkers compared the effects of a combination of intraaortic balloon counterpulsation and intravenous nitroglycerin during the acute phase of infarction with conventional therapy without these interventions. Although the clinical outcomes were similar for both therapeutic groups, patients treated with the ventricular unloading regimen exhibited less echocardiographic evidence of lengthening of the noninfarct segment. Intravenous nitroglycerin, known to have profound dose-dependent acute effects on left ventricular filling pressure, arterial pressure, and regional myocardial blood flow has been shown, both in experimental animals and patients, to be associated with a reduction in infarct size. Jugdutt and Warnica recently reported a randomized trial of placebo versus a carefully titrated regimen for nitroglycerin administration initiated within 12 hours of onset of pain in 310 patients. Creatinine kinase determinations of infarct size again confirmed the effectiveness of appropriately administered acute nitroglycerin in salvaging myocardium. An important aspect of this trial was the use of echocardiographic end points within the first 10 days of the infarction to evaluate topographic changes of the left ventricle. The conventionally treated group showed echocardiographic evidence of infarct expansion that was not observed in the patients treated for approximately 2 days with titrated intravenous nitroglycerin (Figure
5). Although it is difficult to determine whether the beneficial effects of nitroglycerin resulted from limitation of infarct size, reduction in expansion of the infarcted region, or both, the active therapy group had a long-term improvement in clinical outcome.

The potential to favorably influence the process of long-term ventricular enlargement after infarction by pharmacological therapy has been demonstrated in animals and is currently receiving considerable attention in patients. In an animal model of long-term infarction, we tested the hypothesis that the ACE inhibitor captopril would favorably alter the loading conditions on the left ventricle and reduce the progressive enlargement regularly observed. Long-term therapy begun long after any reduction in infarct size was possible was associated with maintenance of cardiac output from a less-dilated ventricular cavity. The groups treated with ACE inhibitor had lower left ventricular operating volumes as a result of both reduced distension (filling pressure) as well as an actual shift to the left (remodeling of left ventricular pressure-volume relation) (Figure 6).

In this same experimental model of myocardial infarction and ventricular dysfunction, the risk of death during long-term follow-up was exponentially related to the extent of histological damage. Long-term therapy with captopril commencing 14 days after coronary ligation was associated with prolongation of survival. Analysis of subgroups using predefined criteria for histological damage demonstrated that the greatest improvement in survival was observed in the group with moderately sized infarcts (20–40% of the left ventricle), the same group in which earlier studies had demonstrated the greatest attenuation of ventricular enlargement with long-term therapy. These studies in the experimental infarct model emphasized that therapy to alter ventricular remodeling after myocardial infarction can, in fact, influence survival. We postulated that ventricular enlargement and dysfunction might favor the establishment of a positive feedback system whereby increases in systolic and diastolic wall stresses promote further ventricular enlargement that, according to La Place’s law, will further augment wall tension. Treatment with an ACE inhibitor was initiated to reduce the augmented internal load that the damaged ventricle sustains in an attempt to reduce wall stress and the resultant progressive enlargement. Captopril therapy was associated with both a reduction in arterial pressure as well as left ventricular end-diastolic pressure. In this same long-term infarct model in the rat, Raya and coworkers demonstrated that long-term captopril therapy resulted in a lower mean circulatory filling pressure, in part attributed to both an augmentation in venous compliance and a reduction in blood volume. These effects on blood volume and venous capacitance produced by long-term captopril therapy were not observed in infarcted animals treated in the long term with equihypotensive doses of hydralazine that did not result in attenuation of ventricular enlargement. In contrast to arterial dilators such as hydralazine, ACE inhibition increases venous capacitance and has several additional actions that blunt the neurohumoral response to ventricular dysfunction, alter intrarenal hemodynamics, and promote sodium excretion resulting in reductions of both preload and afterload.
These observations in experimental animals were then extended to patients. Left ventricular volumes and function were measured approximately 3 weeks after infarction in survivors of transmural anterior infarcts. They were then randomized to receive either captopril or placebo in addition to conventional therapy. As would be anticipated, pronounced left ventricular enlargement and deformation had already occurred by 3 weeks. Although placebo-treated patients showed further ventricular enlargement at 1 year, captopril-treated patients did not. These paired left ventriculograms after anterior infarction showed a pronounced heterogeneity in volume enlargement among patients. In the patients receiving placebo, the predictors of enlargement were the extent of wall motion abnormality (akinesis and dyskinesis) at the time of the baseline measurement and, as previously discussed, the patency of the vessel supplying the infarcted region, that is, the left anterior descending artery (Figure 7). These results confirmed the animal studies showing that ventricular enlargement can be a progressive process after anterior Q wave infarction and that this process can be attenuated by long-term captopril therapy. In addition to the improvement in the primary ventriculographic end point, captopril treatment was associated with prolonged exercise capacity, particularly in the subgroup with the most distorted ventricles at baseline.

Sharpe and coworkers broadened the eligibility criteria and studied ventricular enlargement in patients with inferior as well as anterior Q wave infarctions, all with left ventricular baseline dysfunction (ejection fraction, <45%). Using serial echocardiographic measurements of left ventricular volumes, they demonstrated that placebo- and furosemide-treated groups had progressive ventricular enlargement that was not observed in patients treated with captopril therapy.

These beneficial effects of ACE inhibition therapy in preventing progressive ventricular enlargement after myocardial infarction in experimental animals and patients provided the rationale for the ongoing multicenter clinical trial Survival and Ventricular Enlargement (SAVE). This study is testing the hypothesis that the long-term administration of captopril to survivors of infarction with left ventricular dysfunction (radionuclide ejection fraction, ≤40%) but without clinical manifestations of heart failure will reduce mortality and prevent deterioration in left ventricular function after infarction.

**Summary**

The acute and long-term changes in ventricular topography (ventricular remodeling) after myocardial infarction are important processes affecting ventricular function and survival. Therapy to limit infarct size, enhance scar formation, reduce or prevent infarct expansion, and reduce ventricular wall stress can all favorably impact on the topographic changes of the ventricle that has sustained an infarction. Although a great deal of attention has been appropriately focused on the limitation of the initial insult during a myocardial infarction, the more insidious ventricular remodeling can also have an important impact on the ultimate outcome after infarction. We believe that efforts to affect left ventricular remodeling are at an early stage of development and that further basic and clinical research in this field will improve the long-term outcome of patients who suffer acute myocardial infarction.

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**Figure 7.** Graph showing volume enlargement from 3 weeks to 1 year after anterior myocardial infarction in patients with occluded infarct-related coronary artery. Patients with fewer wall-motion abnormalities (akinesis+dyskinesis<30%) had less enlargement than those with more severe baseline abnormalities. Patients with therapy with captopril had less ventricular enlargement (p<0.05). (Adapted from Pfeffer MA, Lamas GA, Vaughn DE, Parisi AF, Braunwald E: N Engl J Med 1988;319:80, with permission.)


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**Ventricular Remodeling After Myocardial Infarction**

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