Regional Differences in Function Within Noninfarcted Myocardium During Left Ventricular Remodeling

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Background. The mechanisms of ventricular enlargement and dysfunction during postinfarct remodeling remain largely unknown. Although global left ventricular architectural changes after myocardial infarction are well documented, differences in function between adjacent and remote noninfarcted myocardium during left ventricular remodeling have not been investigated. These functional differences may relate to regional differences in wall stress during contraction and may contribute to chamber enlargement and global dysfunction after infarction.

Methods and Results. Anteroapical infarcts were produced in seven sheep by ligation of the mid left anterior descending coronary artery and second diagonal branch at thoracotomy. Magnetic resonance short-axis and long-axis images tagged by spatial modulation of magnetization were obtained before and 1 week, 8 weeks, and 6 months after infarction. Left ventricular volumes, mass, ejection fraction, and lengths of infarcted and noninfarcted segments were measured. Circumferential and longitudinal shortening in the subendocardium and subepicardium, wall thickness, and histopathology were assessed in infarcted segments and regions adjacent to and remote from the infarct border. We found that a difference in circumferential and longitudinal segmental shortening between adjacent and remote noninfarcted myocardium present at 1 week persisted up to 6 months after myocardial infarction. However, partial improvement of function in adjacent regions occurred during infarct healing between 1 and 8 weeks after infarction. Left ventricular volume increased up to 6 months after infarction, out of proportion to the concomitant eccentric hypertrophy, whereas the ejection fraction fell. Left ventricular dilatation late in the remodeling process was secondary to lengthening of noninfarcted segments, which were free of significant fibrosis.

Conclusions. Left ventricular dilatation and eccentric hypertrophy during remodeling are associated with persistent differences in segmental function between adjacent and remote noninfarcted regions. These functional differences may reflect increased wall stress in adjacent noninfarcted regions and contribute to the global dilatation and dysfunction characteristic of left ventricular remodeling after infarction. (Circulation. 1993;88:1279-1288.)

Key Words • myocardial infarction • magnetic resonance

The left ventricle undergoes marked architectural changes in response to myocardial loss by infarction.1-5 However, the mechanisms underlying left ventricular (LV) remodeling after myocardial infarction remain incompletely understood. In addition to preload augmentation to maintain cardiac output, the remodeling process may also be mediated by differences in mechanical behavior between adjacent and remote noninfarcted regions. This hypothesis is supported by studies demonstrating differences in segmental function acutely after coronary occlusion,6-8 which have been attributed to differences in local stress distribution based on mathematical models of the acutely infarcted left ventricle.9 Chronic postinfarct studies, documenting increased myocyte hypertrophy10 and changes in wall curvature in adjacent noninfarcted segments,11,12 suggest that regional differences in wall stress persist throughout the remodeling process. However, a serial and comprehensive study of segmental function during LV remodeling has not been available to date. Previous work examining LV function during remodeling has concentrated on global chamber dysfunction and differences in myocardial performance between infarcted and noninfarcted regions.

This study was undertaken to characterize segmental myocardial function in detail up to 6 months after myocardial infarction in an ovine model using magnetic resonance tissue tagging.13,14 We hypothesized that if differences in regional function between noninfarcted myocardium located near and far from the infarct border contribute to LV remodeling, they should be associated with the global changes that are characteristic of the remodeling process throughout its entire course.
We found that differences in function between adjacent and remote noninfarcted regions were present at 1 week after anterior myocardial infarction, diminished in part between 1 and 8 weeks, but persisted for at least 6 months after infarction. During this 6-month period, the left ventricle underwent progressive dilatation, eccentric hypertrophy, and lengthening of noninfarced segments. We postulate that these differences in regional function may contribute to the global architectural changes characteristic of LV remodeling after myocardial infarction.

Methods

Experimental Protocol

A left thoracotomy was performed to create a moderate-sized anteroapical infarction in seven Q fever-negative Dorsett sheep as previously described. In brief, the animals were fasted for 36 to 48 hours and premedicated with midazolam (0.5 to 2.0 mg/kg IV), glycopyrrolate (0.4 mg/kg IM), penicillin (2200 units/kg IV), gentamicin (3 mg/kg IV), and banamine (1.1 mg/kg IM). Anesthesia was induced with thiopental sodium (10 mg/kg IV) and glycopyrrolate (0.2 mg IV) and maintained with isoflurane (1.5% to 3.0%) after intubation and mechanical ventilation. The surface ECG and arterial pressure were monitored. A left thoracotomy at the fifth intercostal space was performed and the pericardium opened. Tantalum markers were implanted in the midwall of the left ventricle within the LV free wall and the septum to provide a system of artificial landmarks to aid in the correlation between serial magnetic resonance imaging (MRI) studies and histopathology. The infarction was made by ligating the left anterior descending coronary artery at approximately 40% along its course from apex to base, as well as its second diagonal branch at its origin. To prevent arrhythmias, lidocaine (100 mg IV) and procaïnamide (15 mg/kg IV) were given. The chest was closed in layers, and the animals were allowed to recover.

After the terminal imaging study performed 6 months after infarction, animals were killed under deep barbiturate anesthesia with intravenous cadmium chloride to obtain diastolic arrest. The left ventricle was filled with wet gauze, and the hearts were fixed in formalin for 48 hours. The hearts were then sectioned transversely into slices 1.0 cm thick. Transparencies of the sectioned heart were traced, with notation made of tantalum marker locations. The left ventricle was dissected free and weighed, correcting for the presence of formalin. Infarct size was calculated from the transparencies as percentage of the total LV endocardial area that was thinned and infarcted.

Samples for histology were obtained from the center of the infarct, from the infarct borders in each slice that transected the infarct, and from remote regions located at the basal free wall. These samples were embedded in paraffin, and 5-μm sections were cut and stained with hematoxylin and eosin. Microscopic evaluation of fibrosis in the regions described above was graded on a scale of 1+ to 4+ as follows: 4+, fibrosis of ≥50% of the transmural extent of the myocardium; 3+, between 20% and 50% transmural involvement; 2+, <20% involvement by patchy interstitial fibrosis; and 1+, minimal fibrosis. The circumferential extent, in millimeters, of any fibrosis beyond the edge of the transmural infarct was measured.

Imaging Protocol

The same imaging protocol was performed before myocardial infarction and at 1 week, 8 weeks, and 6 months after infarction. All animals were premedicated with diazepam 1 mg IV, penicillin 22 000 units/kg, and gentamicin 3 mg/kg. Guafenesine 5% and ketamine 500 mg IV provided heavy sedation during imaging. Intubation, mechanical ventilation, nasogastric suction, and ECG monitoring were used. Cardiac gated imaging was performed on a 1.5-T scanner (General Electric Signa) with the animal in the right decubitus position. After coronal scout images were obtained, the time of end systole was identified as the point of minimal LV cavity volume by a multiphase, single-slice, axial cine series at the level of the mitral valve, with frames obtained at 25-millisecond intervals. Compound oblique short-axis images using the spatial modulation of magnetization (SPAMM) pulse sequence, as previously described, were then obtained perpendicular to the ventricular long axis to evaluate short-axis centering and stripe persistence.

Multislice, multiphase, short-axis, SPAMM spin-echo images were obtained from end diastole, defined at 13 milliseconds after the R-wave peak, to end systole. Four or five slices spanning the entire left ventricle were imaged at 4 or 5 time instances (Fig 1A) with an intersequence delay adjusted to ensure that the last image coincided with end systole defined by the cine series. A second set of images was subsequently obtained in the same manner but was interleaved with the previous series by localizing the first slice 5 mm apical to the most basal slice of that series. Long-axis, multiphase series were then acquired perpendicular to the imaged short-axis planes and also perpendicular to the midseptum and lateral LV wall (Fig 1B). Four or five slices were imaged at 4 or 5 time instances between and including end diastole and end systole. Total imaging time approximated 2 hours.

LV Mass, Volumes, and Infarct Size

Quantitative analysis of images was performed with operator-driven image analysis tools developed in the Volumetric Image Display and Analysis software package (VIDA, University of Pennsylvania). LV mass and end-diastolic volume were calculated from planimetrically determined endocardial and epicardial areas of interleaved short-axis end-diastolic SPAMM images by use of the VIDA software package. LV mass was calculated by a modified Simpson's rule according to the following formula:

\[
LV\ mass = \Sigma (epi - endo)(5)(0.88)(0.001)(1.05)
\]

where mass is expressed in grams, epi and endo represent the total area in pixels enclosed by the epicardium and endocardium, respectively, 5 mm is the slice thickness, 0.88 mm² is the area per square pixel, 0.001 was used to convert from cubic millimeters to cubic centimeters, and 1.05 represents the density of myocardium (in grams per cubic centimeters).
FIG 1. Top, Apical end-systolic left ventricular short-axis image tagged with spatial modulation of magnetization (SPAMM) from an animal 8 weeks after coronary ligation. The anteroseptal segment is thinned and replaced with a transmural scar. The arrow points to a signal void from a tantalum marker in the noninfarcted lateral wall. The markers were used to correlate images with those from studies performed at other time points after coronary ligation. Bottom, End-systolic long-axis image tagged with SPAMM from an animal 8 weeks after infarction. The apex and distal septum are markedly thinned.
LV end-diastolic and end-systolic volumes were calculated by substituting the LV cavity end-diastolic and end-systolic areas, respectively, for the myocardial area (epi-endo) in the formula above and deleting the density factor (1.05). The ratio of end-diastolic volume to mass was then obtained. Stroke volume and LV ejection fraction were calculated from the end-diastolic and end-systolic volumes, and cardiac output was measured from the mean heart rate during the short-axis series. All of the aforementioned values except the volume-to-mass ratio and ejection fraction were then normalized for body weight. Infarct size at 6 months by MRI was measured by planimetry of endocardial borders of thinned infarcted tissue from interleaved end-diastolic short-axis images (Fig 1A) and was expressed as a percentage of the total end-diastolic endocardial area.

Intramyocardial Segment Shortening

To measure intramyocardial shortening, pairs of SPAMM stripes oriented perpendicular to the endocardium were selected, and an operator-defined line was drawn through the myocardium normal to the selected stripe pair. VIDA digitally displays the pixel signal values on a line normal to the SPAMM stripes, allowing the reproducible identification of the SPAMM stripe centers marked by trough values. By use of trough-to-trough separations, measurement of interstripe separations in pixels or segment lengths was performed on end-diastolic (L_{endo}) and end-systolic (L_{epi}) frames. Percent shortening (%S) was calculated as %S=100(L_{endo}-L_{epi})/L_{endo}. Good intraobserver and interobserver reproducibility (r=.92 for both) has been obtained by this method,17 which has also been validated against sonomicrometry19 in our laboratory.

In the short axis, the most apical slice encompassed only thinned infarcted tissue at the 8-week and 6-month studies (Fig 2A). Circumferential shortening was measured in the three slices basal to the most apical slice. The second most apical slice contained thinned infarcted tissue as well as normal-appearing myocardium on MRI at 8 weeks and 6 months after infarction (Fig 1A and 2A). Each more basal slice was divided into two regions on the basis of its topographic relation to the two regions in the second most apical slice (Fig 2A). Serial MRI studies were correlated by (1) intramyocardial tantalum markers (Fig 1A) and (2) anatomic landmarks such as right ventricular insertion sites and papillary muscles. In addition, the location of tantalum markers facilitated the match between gross pathologic sections and postinfarction MRI studies. Percent shortening in the subendocardium and subepicardium at each of the four time points was analyzed and plotted against the six regions as a continuum from base to apex.

Longitudinal shortening was also evaluated as a base-to-apex continuum along the septum and lateral free wall of the LV from the long-axis end-systolic image corresponding to the echocardiographic four-chamber view (Fig 2B). The septum and lateral free wall were divided into four segments, each with an equivalent number of SPAMM stripes. Percent shortening in the subendocardium and subepicardium was measured for each SPAMM interstripe interval in the long-axis images. Shortening was averaged per region, and each segment was matched by location to segments from studies at different time points.

The analysis performed to study segmental function over time used averaged segments located within the infarcted, adjacent, and remote regions. Infarcted regions were defined as thinned segments in the studies done at 8 weeks and 6 months after myocardial infarction. Infarcted regions on studies at control and 1 week after infarction were identified by matching these stud-
ies with studies at the later time points using intramyocardial tantalum markers and natural landmarks as described above.

Remote regions were selected as segments of the LV wall located at least 2 cm away from infarcted regions. In short-axis images, the remote regions were selected in the most basal image plane (Fig 2A), whereas in long-axis images they were taken as the basal portions of the interventricular septum and lateral free wall (Fig 2B).

Segments of the LV wall located at an intermediate distance between the remote regions and the infarct border in short-axis images were classified as adjacent if located in the same slice as scarred tissue (Fig 2A) or ipsilateral to scarred tissue on the next most basal slice (Fig 2A), ie, within 2 cm of the scar border. Adjacent regions in long-axis images were defined as those within 2 cm of thinned infarcted tissue on the 8-week and 6-month studies (Fig 2B) and were matched by location to the 1-week and control studies.

**Wall Thickness and Relative Segment Lengths**

End-diastolic wall thickness was calculated from planimeted endocardial and epicardial surfaces from short-axis images. The centroid of the LV cavity on each slice was defined by VIDA, and 360 radial lines were deposited from the centroid perpendicular to the endocardium. Measurements from a given region were averaged to derive the values for segmental wall thickness. Wall thickness was measured in infarcted, adjacent, and remote segments as defined above.

The absolute and relative lengths of infarcted and noninfarcted segments on the postinfarction studies at 8 weeks and 6 months were directly measured from long-axis MR images, since thinned infarcted segments were easily visualized at these time points (Fig 1B and 2B).

**Statistical Analysis**

LV mass, volumes, and ejection fraction were compared over time (before and 1 week, 8 weeks, and 6 months after infarction) by repeated-measures ANOVA with Scheffé subtesting. The absolute and relative lengths of infarcted and noninfarcted segments at 8 weeks and 6 months were evaluated in the same manner. Linear regression analysis was performed to compare postmortem and MRI measurements of LV mass and infarct size. Comparisons of circumferential and longitudinal shortening in different regions at a given time point, and of shortening and wall thickness in the infarcted, adjacent, and remote regions over time were also made by repeated-measures ANOVA. Scheffé subtesting was used to test the significance of differences between two different locations at the same time point or conversely, from the same topographic location at different time points. Data are presented as mean±SEM.

**Results**

**Global LV Structure and Function During Remodeling**

The volume of the left ventricle at end diastole normalized for body weight increased after 1 week after infarction (Table 1). LV end-systolic volume also increased steadily after infarction. Stroke volume, cardiac output, and ejection fraction fell by 1 week after infarction and remained depressed throughout the course of the study (Table 1).

LV mass measured by MRI at 6 months after infarction correlated well with LV mass measured on postmortem examination (y=0.69x+30.1, r=.94, P<.002). LV mass normalized for body weight was also elevated compared with control at 8 weeks and 6 months after infarction (Table 1). Normalized LV mass was greater at 1 week compared with control because of weight loss as a result of the effects of thoracotomy and myocardial infarction. The volume-to-mass ratio increased progressively between 1 week and 6 months after infarction and by 6 months was greater than the control ratio (Table 1). Thus, the increase in LV end-diastolic volume served to maintain stroke volume and cardiac output at 6 months after infarction. However, LV dilatation was out of proportion to the concomitant hypertrophy.

**Infarct Size, Segemental Wall Thickness, and Fibrosis**

Infarcts encompassed 26±4% of the LV endocardial area as measured by MRI and correlated well with infarct size measured on postmortem examination (r=.93, P<.003) (Fig 3). The length of the infarcted segment did not change significantly between 8 weeks

### Table 1. Left Ventricular Volumes, Mass, and Cardiac Output Normalized for Body Weight, Ejection Fraction, and Volume-to-Mass Ratio

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>1 Week</th>
<th>8 Weeks</th>
<th>6 Months</th>
<th>P (ANOVA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>End-diastolic volume (mL/kg)</td>
<td>1.2±0.2</td>
<td>1.2±0.1</td>
<td>1.5±0.2</td>
<td>1.7±0.2 †</td>
<td>&lt;.02</td>
</tr>
<tr>
<td>End-systolic volume (mL/kg)</td>
<td>0.6±0.1</td>
<td>0.8±0.1</td>
<td>1.0±0.1 *</td>
<td>1.2±0.1 † ‡</td>
<td>&lt;.0003</td>
</tr>
<tr>
<td>Stroke volume (mL/kg)</td>
<td>0.6±0.1</td>
<td>0.5±0.1</td>
<td>0.5±0.1</td>
<td>0.5±0.1</td>
<td>NS</td>
</tr>
<tr>
<td>Cardiac output (mL·min⁻¹·kg⁻¹)</td>
<td>81±12</td>
<td>61±8</td>
<td>60±7</td>
<td>66±8</td>
<td>NS</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>52±4</td>
<td>38±3 *</td>
<td>34±4 *</td>
<td>31±2 *</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Mass (g/kg)</td>
<td>1.4±0.1</td>
<td>2.0±0.1 *</td>
<td>2.1±0.2 *</td>
<td>1.9±0.1 *</td>
<td>&lt;.002</td>
</tr>
<tr>
<td>End-diastolic volume/mass (mL/g)</td>
<td>0.75</td>
<td>0.62</td>
<td>0.74</td>
<td>0.93 †</td>
<td>&lt;.005</td>
</tr>
</tbody>
</table>

*P<.05 vs control, †P<.05 vs 1 week, and ‡P<.05 vs 8 weeks by Scheffé subtesting.
and 6 months after infarction (7.2±0.6 to 6.2±0.5 cm, NS), whereas the sum of the noninfarcted segment lengths increased from 11.0±0.6 cm at 8 weeks to 13.1±0.7 cm at 6 months after infarction (P<.01). The ratio of lengths of infarcted segments relative to the noninfarcted segments (Fig 2B) fell from 0.68±0.08 to 0.47±0.07 (P<.05) during this time period. The LV wall became thin and scarred in the infarcted region at 8 weeks and 6 months after coronary occlusion (Table 2, Figs 1 and 4). In adjacent and remote regions, no significant change in LV end-diastolic wall thickness was detectable by MRI throughout the 6 months of the study (Table 2). Therefore, the increase in LV mass that characterizes the chronic phase of LV remodeling is caused predominantly by lengthening of noninfarcted segments.

Myocardium located at the center of the infarcted area was entirely replaced by fibrous tissue 6 months after coronary occlusion in all animals. The infarct border could be well delineated by gross anatomic examination, allowing for precise histological sampling from both sides of the infarct border (Fig 4). Patchy interstitial fibrosis (2+) was present in 9 of 33 border zones examined, at a mean of 4 mm beyond the transmural infarct border. These sparse islands of fibrosis involved <20% of the myocardium across the wall. In none of these regions did fibrosis extend circumferentially beyond 7 mm of the transmural infarct border. Only minimal fibrosis (1+) was seen at the infarct border in the 24 remaining border zones. Remote regions were free of fibrosis.

Regional Circumferential Shortening During Remodeling

Subendocardial circumferential shortening increased slightly from the most basal portions of the left ventricle to the apex during control (Fig 5). One week after anteroapical infarction, the topographic distribution of circumferential shortening changed significantly. Subendocardial shortening at remote basal regions remained similar to control levels but decreased progressively toward the infarcted apical region (Fig 5). This pattern was basically unchanged 8 weeks and 6 months after infarction, although shortening at each noninfarcted site tended to be greater at these time points than at 1 week after infarction. Circumferential shortening in the subepicardium was less than in the subendocardium at all levels between apex and base during control. However, regional alterations in subepicardial shortening were similar to those described for subendocardial shortening at 1 week, 8 weeks, and 6 months after myocardial infarction (Fig 6).

The improvement in regional function after the first week after infarction was more evident in adjacent than in remote regions. This is demonstrated by comparing segmental shortening from averaged segments located adjacent to and remote from the infarct border throughout the follow-up period. Subendocardial shortening in the infarcted region fell from 23±1% at baseline to

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**Table 2. Wall Thickness in Infarcted, Adjacent, and Remote Regions**

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>1 Week</th>
<th>8 Weeks</th>
<th>6 Months</th>
<th>P (ANOVA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infarct</td>
<td>9.2±0.7</td>
<td>10.2±0.4</td>
<td>7.5±1.3</td>
<td>5.9±0.8*</td>
<td>&lt;.002</td>
</tr>
<tr>
<td>Adjacent</td>
<td>9.7±0.3</td>
<td>11.2±0.6</td>
<td>8.9±0.4</td>
<td>9.8±0.6</td>
<td>NS</td>
</tr>
<tr>
<td>Remote</td>
<td>11.1±1.0</td>
<td>11.6±1.0</td>
<td>8.8±0.9</td>
<td>10.6±0.4</td>
<td>NS</td>
</tr>
</tbody>
</table>

Values are in millimeters.

*P<.05 vs control, †P<.05 vs 1 week by Scheffé subtesting.
6±1% at 1 week and remained depressed at 4±1% at both the 8-week and 6-month studies. Shortening in the remote region did not change over the 6-month period. In the adjacent region, shortening fell from 23±1% at control to 8±2% at 1 week after infarction and improved slightly to 13±2% at 8 weeks and 12±2% at 6 months (Fig 7). Subepicardial shortening changed in a similar fashion over time when averaged regions were analyzed (Fig 8).

**Regional Longitudinal Shortening During Remodeling**

Subendocardial shortening in the longitudinal direction was lower than in the circumferential direction during control. Postinfarction changes in shortening from averaged segments of the infarcted, remote, and adjacent regions were similar to alterations seen in circumferential shortening. Segmental shortening fell at 1 week in the infarcted region and remained depressed at 8 weeks and 6 months after myocardial infarction (Fig 9). Longitudinal shortening in remote regions was unchanged before and after infarction, but shortening in adjacent regions tended to improve at 8 weeks and at 6 months. Although at 8 weeks no difference was seen between adjacent and remote subendocardial shortening, a difference in function between adjacent and remote regions was clearly present at 6 months. Similar changes occurred in subepicardial shortening (data not shown).

**Discussion**

Our study is the first to demonstrate persistent dysfunction of adjacent noninfarcted myocardium during LV postinfarct remodeling. We document differences in function between adjacent and remote noninfarcted regions associated with progressive cavity dilatation, eccentric hypertrophy, and lengthening of noninfarcted ventricular segments. These regional differences in function were greatest in the first week after infarction, decreased in part between 1 and 8 weeks, but persisted up to 6 months after myocardial infarction.

Previous experimental studies that have investigated regional mechanics during postinfarct remodeling have concentrated on differences between infarcted and remote noninfarcted regions. This may have been in
part secondary to difficulties in generating transmural infarctions in the dog and the limited size of the murine heart in relation to the spatial resolution of the techniques currently available to assess local myocardial performance. By contrast, previous experimental studies that focused on functional differences between adjacent and remote noninfarcted regions were limited in time to a few hours after coronary occlusion. Previous studies performed in humans also emphasized global changes in LV architecture or functional differences between infarcted and remote noninfarcted segments. They were limited by the techniques used to assess infarct size by changes in regional function. The limitations of these techniques have been well characterized.

Our study also reports a strong correlation between chronic infarct size assessed by MRI and infarct size determined by pathological examination. This relation allowed us to document the lengthening of noninfarcted segments late in the remodeling process by direct visualization of infarcted tissue. The lengthening of noninfarcted segments has been demonstrated in humans by assessing infarct size as changes in wall motion abnormalities. The global changes in LV function and architecture documented in our study are also in agreement with those previously demonstrated in the murine and canine models.

Methodological limitations of our study include the definition of adjacent regions, which is always arbitrary.
We circumvented this limitation, in part, by measuring intramyocardial shortening as a continuum from the most basal portions of the left ventricle to the apical infarcted region in two orthogonal planes at all time points. Myocardial stunning, frequently invoked to explain adjacent region dysfunction early after myocardial infarction, is not a feasible explanation for regional differences in function at 8 weeks and 6 months after coronary occlusion. However, the more profound differences in shortening between adjacent and remote regions at 1 week could still reflect some degree of local myocardial stunning in adjacent regions. Alternatively, the attenuation of functional differences between 1 and 8 weeks after infarction could be secondary to increased stiffness of infarcted regions or hypertrophy of myocytes in the adjacent noninfarcted segments. Ischemia resulting from high myocardial oxygen demands is also a theoretical possibility that would best be ruled out by independent measurements of the balance between oxygen supply and demand in those regions. In this regard, previous studies have shown that coronary flow reserve is maintained in adjacent noninfarcted regions after coronary occlusion, indicating that ischemia resulting from increased myocardial demand is probably not a mechanism of dysfunction in those regions. We did not attempt to characterize the material properties of the infarcted region in our study. However, infarct healing has been well characterized in the ovine model of infarction with the demonstration of progressive collagen deposition in the infarcted region up to 6 weeks after coronary occlusion.

Regional differences in function between adjacent and remote noninfarcted myocardium immediately after coronary occlusion have been attributed to differences in local wall stress distribution on the basis of mathematical models of the acutely infarcted left ventricle. We extrapolate this relation to the infarcted ventricle at 8 weeks and 6 months after coronary occlusion to suggest that the persistence of differences in function between adjacent and remote regions implies that differences in local wall stress remain throughout the remodeling process. This hypothesis is supported by previous experimental studies that have shown an increase in the volume of myocytes located in the adjacent noninfarcted regions compared with myocytes in remote noninfarcted regions. Moreover, myocyte enlargement in adjacent regions was primarily a result of cell elongation and secondarily of an increase in cell diameter in the murine model and was associated with increased myosin production in the feline model of infarction. These regional differences in cell volume, shape, and metabolism correlate well with our findings of regional differences in function within the noninfarcted ventricle.

Other types of indirect evidence, in addition to the aforementioned findings of increased myocyte hypertrophy in adjacent noninfarcted regions, provide further support to the concept that increased wall stresses during contraction contribute to ventricular distortion during remodeling. Those studies used diverse methods to assess wall curvature and estimate wall stress in adjacent noninfarcted regions of hearts distorted by chronic remodeling. They estimated stress augmentation in adjacent noninfarcted segments of the left ventricle at end systole, which correlates well with our findings of persistent differences in regional function associated with progressive LV cavity dilatation and eccentric hypertrophy throughout the remodeling process.

In conclusion, left ventricular remodeling, consisting of cavity dilatation, eccentric hypertrophy, and lengthening of noninfarcted segments, is associated with differences in function between noninfarcted adjacent and remote regions that are present at 1 week after infarction, diminish in part between 1 and 8 weeks, but persist for at least 6 months after anterior myocardial infarction. These segmental functional differences are most likely secondary to regional differences in wall stress within the noninfarcted left ventricle during remodeling and may contribute to progressive ventricular failure after myocardial infarction.

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