Infarct Resorption, Compensatory Hypertrophy, and Differing Patterns of Ventricular Remodeling Following Myocardial Infarctions of Varying Size

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OBJECTIVES

We sought to identify advantages of contrast-enhanced magnetic resonance imaging (MRI) in studying postinfarction ventricular remodeling.

BACKGROUND

Although sequential measurements of ventricular volumes, internal dimensions, and total ventricular mass have provided important insights into postinfarction left ventricular remodeling, it has not been possible to define serial, directionally opposite changes in resorption of infarcted tissue and hypertrophy of viable myocardium and effects of these changes on commonly used indices of remodeling.

METHODS

Using gadolinium-enhanced MRI, the time course and geometry of changes in infarcted and noninfarcted regions were assessed serially in dogs subjected to coronary occlusion for 45 min, 90 min, or permanently.

RESULTS

Infarct mass decreased progressively between three days and four to eight weeks following coronary occlusion; terminal values averaged 24% of those at three days. Radial infarct thickness also decreased progressively, whereas changes in circumferential and longitudinal extent of infarction were variable. The ability to define the circumferential endocardial and epicardial extents of infarction allowed radial thinning without epicardial expansion to be distinguished from true infarct expansion. The mass of noninfarcted myocardium increased by 15% following 90-min or permanent occlusion. However, the time course of growth of noninfarcted myocardium differed systematically from that of infarct resorption. Measurements of total ventricular mass frequently failed to reflect concurrent changes in infarcted and noninfarcted regions. Reperfusion accelerated infarct resorption. Histologic reductions in nucleus-to-cytoplasm ratios corresponded with increases in noninfarcted ventricular mass.

CONCLUSIONS

Concurrent directionally opposite changes in infarcted and noninfarcted myocardium can be defined serially, noninvasively, and with high spatial resolution and full ventricular coverage following myocardial infarction. (J Am Coll Cardiol 2004;43:2124–31) © 2004 by the American College of Cardiology Foundation

Although sequential measurements of ventricular volumes, internal dimensions, and total ventricular mass have provided important insights into postinfarction left ventricular (LV) remodeling, it has remained difficult to unravel directionally opposite effects of infarct resorption and myocyte hypertrophy. The magnitude of these changes can vary substantially depending on the size of the infarction, mechanical and hemodynamic factors, and duration of observation (1–4). Areas of infarction can now be defined noninvasively using magnetic resonance imaging (MRI) shortly after administration of gadolinium–based contrast agents (5,6). The present study employed a canine model, first to define the time course of concurrent infarct resorption and increases in noninfarcted muscle mass in the eight weeks following myocardial infarction, and second, to examine potentially differing effects of these changes on commonly used indices of remodeling. A broad range of infarct sizes was obtained by varying the duration of coronary occlusion. Histologic correlations were obtained in additional animals sacrificed at times corresponding to MRI observations.

METHODS

Mongrel dogs of both genders weighing 20 to 30 kg were studied using procedures in accord with the “Position of the American Heart Association on Research Animal Use.” Using sterile technique and procedures previously described (5,6), animals underwent thoracotomy and isolation of the left anterior descending coronary artery (LAD) distal to its first major diagonal branch. The LAD was then occluded for 45 min (n = 5), 90 min (n = 15), or permanently (n = 13). Following occlusion the chest was closed and animals allowed to recover.
MRI. Seventeen animals were serially imaged using contrast-enhanced MRI under isoflurane anesthesia as previously described (5,6). Images were obtained at 3 days, 10 days, and 4 weeks following LAD occlusion in all animals. Eleven animals survived to eight weeks and were also imaged at that time. One 45-min, two 90-min, and two permanent occlusion animals died unexpectedly and a sixth (90-min occlusion) was euthanized after developing hemiparesis. Contiguous 5-mm short axis images encompassing the entire LV (typically 13 to 18 slices) were acquired 15 to 30 min following intravenous administration of 0.3 mmol/kg gadoteridol (Gd-HP-DO3A, ProHance, Bracco) using a T1-weighted IR-Turbo-Flash pulse sequence (7).

Typical imaging parameters included field of view 260 to 280 × 130 to 160 mm², repetition time/echo time 8.0/4.0 ms, inversion time 250 to 350 ms (set to null normal myocardium), in-plane resolution 1.02 to 1.09 × 1.08 to 1.33 mm², slice thickness 5 mm, ~20 k-space lines acquired every other heartbeat. Animals were euthanized after their final imaging sessions using an overdose of sodium pentobarbital followed by potassium chloride and the hearts were retrieved for further study.

**Histologic study.** Eight animals undergoing 90-min occlusion and eight undergoing permanent occlusion were assigned to histologic study. Two animals in each group were sacrificed at 3 days, 10 days, 4 weeks, and 8 weeks following LAD occlusion. A 5-mm short axis LV slice located 2 cm distal to the site of LAD occlusion was used following LAD occlusion. A 5-mm short axis LV slice were sacrificed at 3 days, 10 days, 4 weeks, and 8 weeks after temporary occlusion and eight undergoing permanent occlusion were retrieved for further study. Relative amounts of necrotic myocytes, located 2 cm distal to the site of LAD occlusion was used following LAD occlusion. A 5-mm short axis LV slice were sacrificed at 3 days, 10 days, 4 weeks, and 8 weeks after temporary occlusion and eight undergoing permanent occlusion were retrieved for further study.

![Image](image-url)

**Figure 1.** Parameters used to assess circumferential changes in infarct territory over time. Expansion index = x/y (measured from the midpoints of the papillary muscles); thinning ratio = a/b; endocardial infarct length = S_en; epicardial infarct length = S_ep; mean radial infarct thickness = infarct area (solid area)/ S_en.

Infarcted

Noninfarcted

**Infarct Healing and Ventricular Remodeling**

**Statistical analysis.** Results are expressed as mean ± SEM. Values for infarct mass, noninfarct mass, and total LV mass were initially evaluated using two-factor repeated measures analysis of variance (duration of occlusion and day after occlusion). Because of a significant interaction between the two factors, the analysis was instead performed as a single-factor analysis of variance with each combination of duration of occlusion and day after occlusion considered a factor.
The Bonferroni method of adjusting for multiple pairwise comparisons was used. Relative differences in individual parameters over time were also calculated by expressing absolute values as percentages of their initial (three-day) values. A linear mixed-effects model (S-PLUS 2000) was used to assess whether the time courses of changes in infarcted and noninfarcted mass on MRI were independent processes. Ventricular mass at sacrifice was compared with that computed from the MR images using the method of Bland and Altman (13). All statistical tests were two-tailed, with values of \( p < 0.05 \) considered significant.

**RESULTS**

Table 1 summarizes absolute MRI measurements of infarcted, noninfarcted, and total LV mass for the different durations of occlusion throughout the eight-week study. A typical three-day image data set is shown in Figure 2. As expected, initial infarct size (three days) varied directly with duration of occlusion, averaging 0.9 ± 0.5 g, 14 ± 0.9 g, and 20 ± 4.6 g (corresponding to 2%, 16%, and 23% of LV mass) following 45-min, 90-min, and permanent LAD occlusions, respectively. The mass of the entire LV calculated from eight-week images agreed closely with postmortem LV mass (78 ± 3.9 g vs. 78 ± 3.0 g, \( p = NS \), bias 1.0 ± 2.1%).

Sequential changes in infarcted, noninfarcted, and total LV mass at 3 days, 10 days, 4 weeks, and 8 weeks after infarction are shown in Table 1. Values are mean ± SEM. \( n = 5, 7, \) and 5 for 45-min, 90-min, and permanent occlusion groups at 3 days, 10 days, and 4 weeks, and \( n = 4, 4, \) and 3 at 8 weeks, respectively.

**Table 1.** Noninfarcted (Nonhyperenhanced), Infarcted (Hyperenhanced), and Total LV Masses (Noninfarcted Plus Infarcted) at 3 Days, 10 Days, 4 Weeks, and 8 Weeks After Infarction

<table>
<thead>
<tr>
<th>Time After Infarction</th>
<th>3 Days</th>
<th>10 Days</th>
<th>4 Weeks</th>
<th>8 Weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Permanent occlusion</strong></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Infarcted (g)</td>
<td>20 ± 4.6</td>
<td>17 ± 3.8</td>
<td>9 ± 2.1</td>
<td>5 ± 0.4</td>
</tr>
<tr>
<td>Noninfarcted (g)</td>
<td>70 ± 4.4</td>
<td>71 ± 4.6</td>
<td>75 ± 5.1</td>
<td>76 ± 4.7</td>
</tr>
<tr>
<td>Total LV (g)</td>
<td>90 ± 7.0</td>
<td>88 ± 7.1</td>
<td>83 ± 4.7</td>
<td>81 ± 4.5</td>
</tr>
<tr>
<td><strong>90-min occlusion</strong></td>
<td></td>
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</tr>
<tr>
<td>Infarcted (g)</td>
<td>14 ± 0.9</td>
<td>8 ± 0.7</td>
<td>4 ± 0.4</td>
<td>5 ± 0.2</td>
</tr>
<tr>
<td>Noninfarcted (g)</td>
<td>71 ± 2.7</td>
<td>73 ± 3.1</td>
<td>79 ± 3.0</td>
<td>79 ± 1.3</td>
</tr>
<tr>
<td>Total LV (g)</td>
<td>84 ± 2.6</td>
<td>81 ± 3.2</td>
<td>83 ± 2.7</td>
<td>84 ± 1.1</td>
</tr>
<tr>
<td><strong>45-min occlusion</strong></td>
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</tr>
<tr>
<td>Infarcted (g)</td>
<td>0.9 ± 0.5</td>
<td>0.4 ± 0.2</td>
<td>0.2 ± 0.1</td>
<td>0.2 ± 0.1</td>
</tr>
<tr>
<td>Noninfarcted (g)</td>
<td>66 ± 7.5</td>
<td>66 ± 7.7</td>
<td>67 ± 7.6</td>
<td>72 ± 7.0</td>
</tr>
<tr>
<td>Total LV (g)</td>
<td>67 ± 7.9</td>
<td>66 ± 7.9</td>
<td>67 ± 7.6</td>
<td>72 ± 7.5</td>
</tr>
</tbody>
</table>

LV = left ventricle.

**Figure 2.** Two- and four-chamber long-axis magnetic resonance images and base-to-apex short-axis images in an animal studied three days after coronary occlusion. The anterior ventricular wall shows a nearly transmural area of increased signal intensity (infarction). (Field of view 260 × 160 mm\(^2\), matrix 256 × 120.)
LV mass are presented in Figure 3. Infarct mass decreased progressively in all animals and occlusion groups, but resorption occurred more rapidly in reperfused animals. Terminal values in all animals averaged 24.3% of values at three days. Values at four weeks in the 45-min, 90-min, and permanent occlusion groups averaged 11.8%, 33.2%, and 46.3%, respectively, of those at three days. Values in animals surviving to eight weeks averaged 10.6%, 32.2%, and 22.3% of those at three days.

The mass of noninfarcted myocardium increased systematically with time in the 90-min and permanent occlusion groups. Values at four and eight weeks in the 45-min, 90-min, and permanent occlusion groups averaged 11 ± 8%, 33 ± 2%, and 46 ± 3%, respectively, of those at three days. Values in animals surviving to eight weeks averaged 10 ± 6%, 32 ± 2%, and 22 ± 3% of those at three days.

The mass of noninfarcted myocardium increased systematically with time in the 90-min and permanent occlusion groups. Values at four and eight weeks averaged 111 ± 1% and 117 ± 2% of those at three days in the 90-min occlusion group and 108 ± 2% and 112 ± 4% in the permanent occlusion group. The time course of increase in noninfarcted mass differed from the time course of infarct resorption (p < 0.01). Noninfarcted mass remained unchanged (103 ± 3% at eight weeks) in the smaller infarctions comprising the 45-min occlusion group. Measurements of total mass did not reflect the changes occurring separately in infarcted and noninfarcted regions.

Parameters related to the changing geometry of infarcted and noninfarcted myocardium in 90-minute and permanent occlusion animals (infarcts >3g) are presented in Figures 4 to 6. The LV ejection fractions increased from 27 ± 2% at three days to 44 ± 3% at final study; end-diastolic volumes increased by 11 ± 10% while end-systolic volumes decreased by 13 ± 11%. Infarct resorption consistently involved thinning of the myocardial wall (Fig. 4). Mean radial infarct thickness, which averaged 9.3 ± 1.0 mm at three days, decreased progressively and averaged 3.8 ± 0.6% of three-day values at final study (Fig. 5A). Wall thinning ratios, which averaged 1.3 ± 0.06 at three days, also decreased systematically and averaged 62 ± 5% of three-day values at final study (Fig. 5B).

Changes in the circumferential and longitudinal extents of infarction between three days and final study were variable. The expansion index calculated from LV cavity dimensions (2,12) increased in eight animals by an average of 15 ± 4% (Fig. 5C). All eight showed the expected increase in endocardial infarct arc length (S_en = 121 ± 2% of the value at three days). However, in six of the eight animals the epicardial infarct arc length (S_ep) failed to

Figure 3. Infarcted, noninfarcted, and total left ventricular (LV) mass versus time after infarction. Absolute values are shown in panel A. Panel B depicts relative changes over time; absolute values at three days (the initial values obtained in the study) were designated 100% and subsequent values expressed as percentages of the three-day values. (n = 5, 7, and 5 for 45-min, 90-min, and permanent occlusion groups, respectively, at 3, 10, and 28 days; n = 4, 4, and 3 for 45-min, 90-min, and permanent occlusion groups at 56 days) (a = p < 0.05 vs. day 3, b = p < 0.05 vs. day 10, c = p < 0.05 vs. day 28; x = p < 0.05 vs. 45-min occlusion, y = p < 0.05 vs. 90-min occlusion).
increase; radial thinning occurred without epicardial infarct expansion (Fig. 5D) (Sep = 101 ± 1% of the value at three days). The longitudinal extent of infarction and long-short axis ratio also did not change over time in these animals (longitudinal extent = 98 ± 2% and long-short axis ratio = 97 ± 7% of three-day values).

Three animals that underwent permanent LAD occlusion and had large transmural infarctions (16, 22, and 35 g) showed a different pattern (Figures 5C to 5E), with systematic decreases in the final values of expansion index (88 ± 4% of three-day values), circumferential endocardial (67 ± 3%) and epicardial infarct arc length (74 ± 3%), longitudinal extent of infarction (67 ± 2%), long-/short-axis ratio (80 ± 6%), and mean radial infarct thickness (55 ± 5%). Figure 6 shows a three-dimensional rendering of changes in one of these animals.

Figure 7 indicates more rapid resolution of necrotic tissue and deposition of connective tissue in infarcts reperfused after 90-min occlusions than in nonreperfused infarcts. The time course of resorption of hyperenhanced areas was directly related to the removal of necrotic tissue and inversely related to the deposition of connective tissue. Nucleus-to-cytoplasm ratios in remote noninfarcted regions decreased at similar rates in animals with 90-min and permanent occlusions, concomitant with the increases in noninfarcted ventricular mass observed in animals undergoing serial imaging (Fig. 3).

**DISCUSSION**

The complexity of architectural alterations in ventricular remodeling has been emphasized by Pfeffer (2,3) and is evident in the diversity of findings in the present study. The ability of MRI to separate infarcted and noninfarcted tissue serially and noninvasively with high spatial resolution offers several advantages. Infarctions can be localized precisely and their magnitudes quantified over the full range of infarct size. The pattern and time course of infarct resolution can be determined in individual cases. Geometric patterns of resorption, such as relative contributions of radial thinning and changes in circumferential and longitudinal dimensions, can be defined. Hypertrophy of viable myocardium can be identified when total LV mass is not increasing, and can be quantified throughout the period of infarct resolution. Thus, MRI can add appreciably to information available with approaches utilizing internal ventricular dimensions, cavity geometry and volumes, and total LV mass.

Measurements of infarct size in the first few weeks following infarction need to take into account what Reimer and Jennings (14) have termed the “changing anatomic reference base of evolving myocardial infarction.” In the 1995 canine study by Richard et al. (15), edema, hemorrhage, and inflammation within infarcts caused infarct sizes to increase by 20% to 30% during the first four days following proximal circumflex occlusion. The authors...
termed this process “early infarct expansion.” The magnitude of their early increase measured pathologically is similar to the increase in MRI hyperenhanced area reported by Rochitte et al. (16) in dogs between 2 and 48 h following coronary occlusion. Infarct sizes decreased progressively following early infarct expansion in the study of Richard et al. (15) as necrotic tissue was replaced by collagenous scar. Values at six weeks averaged only 35% to 40% of values at four days. Percent decreases in size over the entire six-week period varied inversely with initial infarct size, raising the possibility that initially smaller infarcts result in disproportionately smaller final scars (15).

Time-related changes in infarct size in the present study seem comparable to those observed by Reimer and Jennings (14). Initial MRI measurements at three days no doubt included early infarct expansion similar to their studies (14,15) and that of Rochitte et al. (16). Subsequent MRI measurements then also decreased progressively, as necrotic myocardium, inflammatory cells, and residual edema and hemorrhage were cleared and replaced by scar tissue. Measurements averaged 11%, 33%, and 44% of three-day values at four weeks and 10%, 32%, and 22% at eight weeks in 45-min, 90-min, and permanent occlusion groups, respectively. Thus, we view our contrast-enhanced MRI measurements as providing longitudinal determinations of the net effect of factors causing early infarct expansion and subsequent infarct resorption in the same manner as would be available if measurements employing 2,3,5-triphenyltetrazolium chloride staining could be performed serially.

Not withstanding the transient early increases in infarct size caused by edema, hemorrhage, and inflammation, the term “infarct expansion” has been used more frequently to characterize other, later changes in ventricular geometry (2,3). In their original pathologic study, Hutchins and Bulkley (17) described infarct expansion as “acute dilation and thinning of the area of infarction not explained by additional myocardial necrosis.” In a subsequent analysis of >200 patients dying with a single infarction, Pirolo et al. (18) concluded that infarct thinning precedes breaks in the external epicardial contour.

Efforts to identify late infarct expansion in vivo have frequently employed an “expansion index” derived from a short-axis view of the ventricle at the level of the papillary muscles (Fig. 1) (12,19). Anterior and posterior endocardial segment lengths between the midpoints of the papillary muscles are compared, with the expectation that serial measurements will show a relative lengthening of a segment containing an infarcted area that is expanding. In the present study eight animals showed progressive increases in both expansion index and directly measured infarct endocardial arc length. However, epicardial arc length remained unchanged in six animals, reflecting progressive wall thinning without expansion of the epicardial contour. Thus, MRI infarct measurements allowed this latter situation, which is probably more common in smaller and non-

Figure 6. Three-dimensional rendering of infarct size at three days and eight weeks in a permanently occluded animal. Green inner surface = left ventricular endocardium, wire mesh = epicardium, red = area of infarction. Infarct size decreased from 15 to 4 g while noninfarct mass increased from 65 to 74 g.
transmural infarcts, to be distinguished from expansion as usually defined. It is also of interest that animals with large transmural infarcts showed prominent circumferential and longitudinal resorption as well as radial thinning, with resultant decreases in expansion index and long-axis/short-axis ratio.

The ability of MRI to separate infarcted and viable muscle can also assist in evaluating other commonly used indices of remodeling based on ventricular volumes, internal dimensions, and total ventricular mass. Because infarcts in this study were predominantly non-transmural, full-thickness wall thinning ratios decreased to 62 ± 5% of three-day values, whereas actual infarct thickness fell to 38 ± 6% of three-day values. The possibility of identifying concomitant hypertrophy of viable epicardial muscle deserves further study. In animals that showed decreases in expansion index, increases in non-infarcted muscle mass were obscured by larger concomitant decreases in infarct size, i.e., total ventricular mass decreased. The consistent ability of MRI to achieve full ventricular coverage also facilitates three-dimensional analysis of changing infarct size (Fig. 6).

The data in Figure 7 are consonant with pathologic observations of Richard et al. indicating that reperfusion can accelerate infarct resorption (15). Although reperfused infarcts also resorbed more rapidly than non-reperfused infarcts in the present study, this finding was probably influenced by differences in infarct size as well as reperfusion. Our observed reductions in the nucleus-to-cytoplasm ratio (Fig. 7, lower panel) correspond to the MRI increases in non-infarct mass (Fig. 3, middle panels), a parameter that has not been able to be assessed directly in previous studies.

In summary, concurrent directionally opposite changes in infarcted and noninfarcted myocardium can be defined serially, noninvasively, and with high spatial resolution and full ventricular coverage following myocardial infarction. The capability is applicable to a broad range of infarct size and should allow improved characterization of ventricular remodeling in relation to infarct resorption and expansion, postinfarction hypertrophy, evolving regional muscle geometry, and indices based on ventricular volumes and internal dimensions.

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