Restraining Infarct Expansion Preserves Left Ventricular Geometry and Function After Acute Anteroapical Infarction

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Background—Expansion of an acute myocardial infarction predicts progressive left ventricular (LV) dilatation, functional deterioration, and early death. This study tests the hypothesis that restraining expansion of an acute infarction preserves LV geometry and resting function.

Methods and Results—In 23 sheep, snares were placed around the distal left anterior descending and second diagonal coronary arteries. In 12 sheep, infarct deformation was prevented by Marlex mesh placed over the anticipated myocardial infarct. Snared arteries were occluded 10 to 14 days later. Serial hemodynamic measurements and transdiaphragmatic quantitative echocardiograms were obtained up to 8 weeks after anteroapical infarction of 0.23 of LV mass. In sheep with mesh, circulatory hemodynamics, stroke work, and end-systolic elastance return to preinfarction values 1 week after infarction and do not change subsequently. Ventricular volumes and ejection fraction do not change after the first week postinfarction. Control animals develop large anteroapical ventricular aneurysms, increasing LV dilatation, and progressive deterioration in circulatory hemodynamics and ventricular function. At week 8, differences in LV end-diastolic pressure, cardiac output, end-diastolic and end-systolic volumes, ejection fraction, stroke work, and end-systolic elastance are significant (P<0.01) between groups.

Conclusions—Preventing expansion of acute myocardial infarctions preserves LV geometry and function. (Circulation. 1999;99:135-142.)

Key Words: ventricles ■ remodeling ■ myocardial infarction

Many variables affect ventricular remodeling after acute myocardial infarction. Size, transmurality, and infarct location are major variables; loading conditions, previous scar, revascularization of occluded vessels, and ACE inhibitors are among other important variables. Nearly 70% of all infarctions are transmural, 54% are anterior, and 35% to 42% of anterior infarctions develop slippage between myocytes to produce infarct expansion and thinning. Ventricular dilatation ceases after a few days in well-compensated hearts with small, minimally expansive infarcts. In patients with expanding infarctions and more severe left ventricular (LV) dysfunction, the prognosis is ominous, because progressive LV dilatation and functional deterioration continue for weeks, months, and even years.

Little is known of the material properties of healing myocardial infarctions, yet relative stiffness of the healing infarct influences mechanical forces affecting ventricular remodeling and performance. On the basis of infarct fibrosis, hydroxyproline content, and uniaxial stress extension studies, clinicians generally conclude that infarcts stiffen. However, this conclusion is inconsistent with the natural history of expanding infarctions and is not confirmed by biaxial stress extension studies of ovine infarctions. Mathematical models predict preservation of LV shape and resting function by preventing infarct expansion, but this prediction has not been tested in sophisticated finite-element models or demonstrated by serial measurements of postinfarction ventricular function. This study tests the hypothesis that restraining infarct expansion preserves ventricular geometry and resting function in a sheep model of acute anteroapical infarction that consistently progresses to LV aneurysm.

Methods

Surgical Protocol

Twenty-three healthy, Dorsett hybrid sheep were induced, intubated, anesthetized with isoflurane 1.5% to 2%, and ventilated with oxygen (Drager anesthesia monitor, North American Drager). All animals received glycopyrrolate 0.4 mg IV and cefazolin 1 g IV. Animals were treated in compliance with the Guide for the Care and Use of Laboratory Animals (NIH publication No. 85-23) as revised in 1985.

By use of aseptic technique, polypropylene snares were placed around the homonymous (designated LAD in this article) and second diagonal (D2) coronary arteries from the apex via left anterolateral thoracotomy. An ultrasonic flow probe (Transonic...
Systems, Inc) was placed around the aortic root. Two epicardial pacemaker wires were sewn to the right atrium. Group assignment was random; 11 animals served as controls (group 1). In 12 animals (group 2), Marlex mesh, a nonabsorbable, monofilament, knitted polypropylene mesh used for hernia repair, was sutured over the precise location of the expected anteroapical infarction of 0.23 of LV mass.14 The wound was closed, and the animals recovered.

**Baseline Data**

After 10 to 14 days, sheep were anesthetized with isoflurane 1% to 2%, intubated, and placed supine. Surface ECGs and arterial blood pressure were monitored continuously. A Swan-Ganz catheter (313h-TFr Baxter Healthcare Corp) was introduced via the left internal jugular vein. A high-fidelity pressure transducer (Spe-350, Millar Instruments Inc) was inserted from the femoral artery into the LV (Hewlett-Packard 7853c monitor). Animals were disconnected from the ventilator, and the heart was atrially paced at 120 bpm for all measurements and echocardiograms.

**Echocardiography**

Subdiaphragmatic 2-dimensional echocardiographic images were obtained through a sterile, midline laparotomy with a 5-MHz. probe (Hewlett Packard 77020A) and were recorded on 0.5-in videotape at 30 Hz (Panasonic AG-6300 VHS Recorder, Matsushita Electric Industries Co Ltd). LV short-axis images at 3 levels (at the tips of the papillary muscles, at the bases of the papillary muscles, and at the apex) and 2 orthogonal long-axis views were obtained. As the LV aneurysm developed, the ventricular long axis angulated; therefore, the apical short-axis image was not always parallel to other short-axis images. LV apical long-axis views were used to calculate LV cavity volumes by biplane Simpson’s rule.17 In addition, serial echocardiographic measurements were made of LV cavity diameter (at the tips of the papillary muscle) and LV long-axis cavity length to assess LV cavity shape (defined as the ratio of the short axis to long axis) at all time points in all animals. LV wall thickness was measured from short-axis images at the level of the papillary muscle bases at baseline and in infarct and remote zones at end diastole and end systole. Wall thickness was also measured in the apical short axis at 8 weeks. Myocardial infarct length was measured as the length of LV cavity perimeter that was either akinetic or dyskinetic (A/D); this A/D length as a percentage of the total cavity perimeter was calculated.13 Last, the length of cavity perimeter from the insertion of the aortic valve leaflets to the edge of the A/D segment in the anterior wall was measured immediately after infarction through 8 weeks.

**Stroke Work**

LV stroke work (SW) was measured from simultaneous measurements of stroke volume and LV pressure16: SW (ergs) = LVA (mm Hg–beat) × SV (ml/beat) × 1330, where LVA is the area under the LV pressure trace, SV is stroke volume as determined by the aortic flow probe, and beat is time in seconds. Measurements were repeated 5 times; means were used for subsequent analyses.

**Slope of the Stroke Work–LV End-Diastolic Pressure Relationship**

A 50-mL Fogarty catheter (US Catheter and Instrument Co) was placed via the jugular vein into the inferior vena cava under fluoroscopic guidance and inflated to decrease ventricular preload. LV pressure and stroke volume were measured over the subsequent 10 beats, and stroke work was plotted against left ventricular end diastolic pressure (LVEDP).15 The relationship was plotted for all 10 beats; correlation coefficients were calculated; all were >0.94, and most were 0.99. Caval occlusions were repeated 5 times, and mean slopes were recorded.

**End-Systolic Elastance**

End-systolic elastance (Ees) was measured by use of an occlusive balloon in the ascending aorta as previously described and validated.15 A custom-made 50-mL intra-aortic balloon (Datascope, Inc) was placed during fluoroscopy in the aortic root from the femoral artery and was connected to a System 90-T intra-aortic balloon pump (Datascope Inc). The balloon was triggered to inflate during diastole and to remain inflated during the following contraction. The balloon produced an isovolumic contraction (verified by flow probe). Using custom software, we constructed a pair of pressure-volume relationships from simultaneous pressure and flow tracings of the last ejecting and first isovolumic contraction19 and assumed no change in end-diastolic volume.15 The end-systolic pressure-volume relationship (ESPVR) or Ees, was drawn from the peak isovolumic pressure-volume point tangential to the left upper corner of the pressure-volume loop of the ejecting contraction. Balloon inflation was repeated 5 times; absolute LV volume was not measured. Ees values obtained from 2 pressure-volume relationships (nonoccluded and completely occluded) were compared with mean values obtained from families of 4 partially occlusive pressure-volume loops created by varying volume in the ascending aortic balloon for 6 sheep at baseline and 2 sheep throughout the entire 8-week study (n = 14). Results showed that average Ees values obtained by both methods differed by 3.4 ± 1.3%, and slopes were not significantly different by paired t test (P = 0.69). Thereafter, all Ees measurements were made by the complete occlusion method described above.

**Infarction**

After baseline data had been obtained, the previously placed exterorized subcutaneous snare wires were tightened sequentially. Arrhythmias were rigorously monitored and controlled by an infusion of lidocaine 2 mg/min and bolus doses of bretyllium 5 mg/kg and magnesium 0.5 g before infarction and esmolol 0.5 to 2.0 mg/kg after infarction. When hemodynamic measurements stabilized (~1 hour), postinfarction measurements were made. The laparotomy was closed.

**Follow-Up Studies**

Identical measurements were made at 1, 2, 5, and 8 weeks after infarction. Only 9 measurements (5 mesh, 4 controls) were made at 1 week; all surviving sheep had measurements at the other time intervals. After week 8, the animal was euthanized (potassium chloride 80 mEq). The heart was excised, and the LV was opened in the long axis and photographed. Sections were taken for histology.

**Statistics**

Measurements are reported as mean ± SD. Differences between groups are compared by 2-way MANOVA (group, time) with Bonferroni adjustment for repeated measures (SPSS 6.0). When the group effect is significant, 1-way ANOVA is used to determine significant differences at different times in each group separately. If the time effect is significant by 1-way ANOVA, differences between before-infarction measurements and measurements at subsequent times are compared by the paired t statistic. When the group effect is significant, differences between groups at specific times are compared by the unpaired t statistic. Significance is accepted at the P < 0.05 probability.

**Results**

Fifteen sheep (9 control, 6 mesh) completed the 8-week protocol. Two animals in the control group died early after infarction, and 2 in group 2 died between 2 and 5 weeks of arrhythmias. Four sheep in group 2 died after 4 weeks of pneumonia, embolic stroke, or euthanasia for wound complications.7 At week 8, all control animals had evidence of heart failure (rales, lethargy); no mesh animal had evidence of heart failure.

Histological sections of mesh-covered infarcts 2 and 8 weeks after infarction show a nonspecific fibrous reaction surrounding mesh fibers without new vessel ingrowth (Figure 1). The epicardial fibrotic reaction does not progress after 2 weeks (Figure 1).
Echocardiograms in sheep with mesh show normal wall thickness and systolic wall thickening beneath the mesh before infarction. Diastolic wall thickness is similar in both groups (8.9±0.3 [SEM] mm, mesh; 9.2±0.4 mm, control) (P=0.47). At week 8, wall thickness near the infarcted apex was 4.8±0.3 (SEM) mm in group 1 and 6.6±0.2 mm in group 2 sheep (P=0.0004).

Hemodynamic measurements are presented in Table 1. The data indicate progressive deterioration in circulatory function over 8 weeks in group 1 sheep and no significant changes in resting hemodynamics in group 2 sheep except immediately after infarction (Figure 2, Table 1).

LV end-diastolic and end-systolic volumes increase progressively over 8 weeks in control sheep but do not progress after week 1 postinfarction in mesh-treated sheep (Figure 3). At week 8, end-systolic and end-diastolic volumes are significantly smaller in sheep with restrained infarcts (Table 2).

In control sheep, ejection fraction, stroke volume, stroke work, the stroke work–LVEDP relationship, and Ees and stroke volume progressively decrease after infarction, and all values except Ees are significantly less than preinfarction measurements at week 8 (Figure 4, Table 2). In group 2 sheep, stroke volume, stroke work, the stroke work–LVEDP relationship, and Ees do not differ significantly from baseline measurements at any time after infarction. Ejection fraction decreases early after infarction but does not decrease further after the first week (Table 2).

Figures 5 and 6 illustrate long-axis echocardiograms before infarction and at 1 and 8 weeks after infarction in control and mesh-treated sheep. The mesh-restrained infarct does not expand, whereas the unrestrained infarct expands asymmetrically into an anteroapical aneurysm.

MANOVA with adjustment for repeated measures showed a significant time effect (P<0.05) for 25 of 34 echocardiographic variables measured; however, only 5 variables were significantly different between groups when analyzed without baseline measurements (Table 3). Differences in LV diastolic cavity shape between groups approached statistical significance at 8 weeks (P=0.055) (Table 3). In mesh-treated sheep, infarct expansion was less over time in control animals and the contractile segment of the anterior wall was greater (Table 3).

Figure 7 is a photograph of a normal ovine heart, a mesh-constrained anteroapical infarction, and an untreated anteroapical infarction at week 8. The shapes of the mesh-constrained infarcted heart and the uninfarcted normal heart are similar.

**Discussion**

A patch of Marlex mesh applied before infarction overcomes the technical obstacle of restraining infarct expansion. The ensuing fibrosis prevents infarct expansion, does not change baseline wall thickness, and has minimal impact on surround-
ing myocardium. Consistency of ovine coronary arterial anatomy between sheep and lack of preformed collateral vessels permit accurate prediction of infarct size and location. Although the method has no therapeutic value, mesh permits a test of our hypothesis.

Prevention of infarct expansion attenuates a decrease in ejection fraction, prevents aneurysm formation, and preserves resting ventricular function. The ventricle retains its normal conical shape despite loss of 0.23 of LV mass. In the mesh group, dimensional, hemodynamic, and functional consequences of the infarct do not progress after 1 or 2 weeks. Exercise reserve may be reduced, but resting ventricular geometry and function are preserved and progressive ventricular deformation is aborted.

Expanding acute anterior infarctions produce progressive deterioration in ventricular function, dilatation, and eventually heart failure in both patients and sheep. The sheep model may exaggerate and accelerate this scenario, but in both species, there is little evidence that either the size or function of the ventricle stabilizes or that the remodeling process ends until regional expansion ends.

The progressive deterioration in ventricular function is best explained by ongoing involvement of viable, border-zone myocardium. Ischemia rapidly reduces end-systolic wall thickness and, by Laplace’s law, increases end-systolic circumferential and meridional wall stresses. Increased regional wall stresses favor infarct expansion, but the amount of

### TABLE 1. Mean±SD of Measured Hemodynamic Parameters

<table>
<thead>
<tr>
<th>Measurement and Group</th>
<th>Before Infarct</th>
<th>After Infarct</th>
<th>1 Week</th>
<th>2 Weeks</th>
<th>5 Weeks</th>
<th>8 Weeks</th>
<th>Time</th>
<th>Group</th>
<th>Interaction</th>
<th>P, Two-Way MANOVA</th>
<th>P, ANOVA</th>
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<tbody>
<tr>
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<td>11</td>
<td>12</td>
<td>5</td>
<td>9</td>
<td>9</td>
<td>6</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Mean Art P, mm Hg</td>
<td>75±7</td>
<td>63±6§</td>
<td>60±7§</td>
<td>69±6†</td>
<td>69±4‡</td>
<td>71±5‡</td>
<td>·</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LVEESP, mm Hg</td>
<td>89±10</td>
<td>81±10</td>
<td>79±12*</td>
<td>81±9†‡</td>
<td>78±7§</td>
<td>79±8‡</td>
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<td></td>
<td></td>
<td>&lt;0.001</td>
<td>&lt;0.124</td>
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<td>LVEDP, mm Hg</td>
<td>85±9</td>
<td>78±10</td>
<td>98±12</td>
<td>100±13§</td>
<td>100±12§</td>
<td>94±7</td>
<td>&lt;0.001</td>
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<tr>
<td>CVP, mm Hg</td>
<td>9.6±2.6</td>
<td>11.9±3.2</td>
<td>10.0±5.0</td>
<td>8.2±2.5</td>
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<td>8.3±3.0</td>
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<td>Cardiac output, L/min</td>
<td>2.4±1.0</td>
<td>2.3±0.9</td>
<td>2.0±0.7</td>
<td>2.0±0.8</td>
<td>1.9±0.4</td>
<td>1.6±0.7†</td>
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<td>0.015</td>
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</table>

Art P indicates arterial pressure; LVEESP, left ventricular end-systolic pressure; and CVP, central venous pressure. Group 1 is the control group; group 2 the experimental group. P values are tabulated for time and group effects and interaction (error) by 2-way MANOVA with adjustment for repeated measures.

*P<0.05 between groups by unpaired t statistic; †P<0.01 between groups by unpaired t statistic; ‡P<0.05; §P<0.01 within groups vs baseline value.
TABLE 2. Mean±SD of Measured and Calculated Parameters

<table>
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<tr>
<th>Measurement and Group</th>
<th>Before Infarct</th>
<th>After Infarct</th>
<th>1 Week</th>
<th>2 Weeks</th>
<th>5 Weeks</th>
<th>8 Weeks</th>
<th>P, Two-Way MANOVA</th>
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<td>5</td>
<td>12</td>
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<tr>
<td>End-diastolic volume, mL</td>
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<tr>
<td>1</td>
<td>54.0±11.3</td>
<td>67.5±15.9</td>
<td>78.4±29.9†</td>
<td>86.4±21.9§</td>
<td>91.7±11.9§</td>
<td>98.3±16.0§</td>
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<td>2</td>
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<td>60.1±12.1</td>
<td>80.8±15.1§</td>
<td>75.0±10.2§</td>
<td>76.2±11.5§</td>
<td>78.1±11.5§</td>
<td>&lt;0.001 0.001 0.109</td>
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<tr>
<td>End-systolic volume, mL</td>
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<td>1</td>
<td>28.3±6.9</td>
<td>39.5±9.8</td>
<td>54.3±28.7§</td>
<td>68.1±17.6§</td>
<td>66.3±11.1†</td>
<td>75.9±18.8§</td>
<td>&lt;0.001 0.001 0.109</td>
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<td>2</td>
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<td>34.7±8.4‡</td>
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<td>Ejection fraction, %</td>
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<td>42.5±5.5‡</td>
<td>36.7±14.7§</td>
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<td>Stroke work, ergs×10³</td>
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<td>244±101</td>
<td>178±73‡</td>
<td>170±52§</td>
<td>139±54‡</td>
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<td>SW-LVEDP slope, ergs×10³/mm Hg</td>
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<td>24.6±7.9§</td>
<td>26.3±10.4†</td>
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<td>End-systolic elastance, mm Hg/mL</td>
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<td>1</td>
<td>4.7±2.4</td>
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<td>0.128</td>
</tr>
</tbody>
</table>

P values are tabulated for time and group effects and interaction (error) by 2-way MANOVA with adjustment for repeated measures.

*P<0.05 between groups by unpaired t statistic; †P<0.01 between groups by unpaired t statistic; ‡P<0.05; §P<0.01 within groups vs baseline value.

expansion also depends on material properties of the new infarction. If the infarct expands, the radius of curvature of infarct and adjacent border zone also increases; elevated wall stresses in both regions cause progressive wall thinning. Border-zone thinning decreases myocyte contractility, increasing segmental length, and pulls myocardium toward the expanding infarct. Mature scar may stabilize the center of the infarct, but in the border zone, the process may continue until expansion stops or heart failure and death intervene.

Material properties of the normal, beating heart are heterogeneous, anisotropic, and possibly even time-dependent. Compliance of the infarct initially decreases after infarction because of edema and necrotic myocytes, but often increases later. Late changes in infarct compliance vary with infarct size, location, transmurality, and other factors and reflect changes in infarct material properties and regional wall stresses in the remodeling ventricle. In sheep and perhaps in humans, differences in infarct expansion between anterior and posterior infarctions of similar sizes may be explained by differences in material properties rather than initial differences in systolic wall stress. Stable ventricular geometry requires a balance between myocardial material properties resisting expansion and ventricular wall stresses and strains. It follows that when regional wall stresses increase, myocardium must...
Figure 5. A, Long-axis echocardiogram at end systole before infarction; B, 1 week after infarction; and C, 8 weeks after infarction in a control sheep. Arrows and arrowheads mark junctions between dyskinetic segment and contracting myocardium on anterior wall (arrow) and posterior wall (arrowhead). LA indicates left atrium; LV, left ventricle.

Figure 6. A, Long-axis echocardiogram at end systole before infarction; B, 1 week after infarction; and C, 8 weeks after infarction in a mesh-treated sheep. Arrows, arrowheads, and abbreviations as in Figure 5.
either stiffen to prevent or minimize strain or, alternatively, deform in the direction of applied stresses.

The clinical benefit of preventing infarct deformation and preserving ventricular geometry shown in this study focuses attention on the extracellular matrix of healing infarctions. Late reperfusion (6 to 12 hours after onset of chest pain) attenuates infarct expansion and improves survival but does not rescue myocytes. Initially, hemorrhage and edema may stiffen the infarct; later, revascularization may alter the molecular and cellular responses in the extracellular matrix. At present, no surgical procedures exist to limit expansion of acute infarctions, but given the need, operations can be developed.

Limitations of This Study
The relevance of the sheep model to transmural anteroapical infarctions in humans cautions against extrapolation of these conclusions to patients. The sheep model avoids many confounding variables associated with human anteroseptal infarctions, but these variables may be relevant to clinical care.

Mesh applied before infarction may stimulate an inflammatory reaction within the underlying myocardium and alter the remodeling process independently of external restraint. At this time, this possibility lacks supportive evidence. It is acknowledged that the mesh also covered some border-zone tissue, but the amount is small and logically should reduce rather than enhance LV performance.

This study raises but does not address the issue of how best to prevent expansion of acute myocardial infarctions.

Acknowledgments
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### Table 3. P Values Within Groups Calculated by One-Way ANOVA

<table>
<thead>
<tr>
<th>Parameter and Group</th>
<th>Baseline</th>
<th>Post</th>
<th>2 Weeks</th>
<th>5 Weeks</th>
<th>8 Weeks</th>
<th>P Value Within Groups</th>
<th>P Value Between Groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVID/length ratio (diastole)</td>
<td>0.49±0.05</td>
<td>0.42±0.04</td>
<td>0.44±0.04</td>
<td>0.47±0.05</td>
<td>0.43±0.05</td>
<td>0.001</td>
<td>0.95</td>
</tr>
<tr>
<td>Length LV-WMA (systole), cm</td>
<td>6.84±1.0</td>
<td>7.80±1.34</td>
<td>7.94±1.30</td>
<td>8.04±1.35</td>
<td>0.18</td>
<td>0.04</td>
<td>0.46</td>
</tr>
<tr>
<td>Length base to WMA (systole), cm</td>
<td>4.50±0.68</td>
<td>4.11±0.50</td>
<td>4.57±0.84</td>
<td>4.59±0.58</td>
<td>0.48</td>
<td>0.07</td>
<td>0.95</td>
</tr>
</tbody>
</table>

LVID indicates left ventricular internal diameter at base of papillary muscles. The ratio LVID/length is an index of LV cavity shape and shows significant change only in control sheep after infarction. WMA, wall motion abnormality.

P values between groups were calculated without baseline measurements by 2-way ANOVA and the unpaired t statistic for group effects, P<0.05. In addition to these measurements, significant between-group differences occurred in length of WMA/long-axis perimeter in systole (P<0.01) and in length to WMA/long-axis perimeter in systole (P<0.001).

Figure 7. Photograph of longitudinally cut left ventricles of A, Normal sheep; B, Mesh-treated infarcted sheep; and C, Control infarcted sheep.
Restraining Acute Myocardial Infarction

References


Restraining Infarct Expansion Preserves Left Ventricular Geometry and Function After Acute Anteroapical Infarction

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