Prevention of Ischemic Mitral Regurgitation Does Not Influence the Outcome of Remodeling After Posterolateral Myocardial Infarction

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OBJECTIVES
This study was designed to test the hypothesis that ischemic mitral regurgitation (IMR) results from, but does not influence, the progression of left ventricular (LV) remodeling after posterolateral infarction.

BACKGROUND
Surgical correction of chronic IMR is being increasingly recommended.

METHODS
Three groups of sheep had coronary snares placed around the second and third obtuse marginal coronary arteries. Occlusion of these vessels in the control group resulted in progressive IMR over eight weeks. In a second group, Merseline mesh was fitted to cover the exposed LV before infarction. In a third group, a ring annuloplasty was placed before infarction to prevent IMR. Remodeling and degree of IMR were assessed with echocardiography at baseline and at 30 min and two, five, and eight weeks after infarction.

RESULTS
Eight weeks after infarction, mean IMR grade was significantly higher in control animals than mesh and annuloplasty animals. At eight weeks, LV end-systolic volume and end-systolic muscle-to-cavity-area ratio (ESMCAReR) were significantly better in mesh-treated sheep than in control sheep; also, at eight weeks, ESMCAReR and akinetic segment length were significantly better in mesh-treated sheep than in annuloplasty sheep. Ejection fraction was significantly higher in the mesh than the annuloplasty group. There was no significant difference in any measure of remodeling between the annuloplasty and control groups.

CONCLUSIONS
Prophylactic ventricular restraint reduces infarct expansion, attenuates adverse remodeling, and reduces IMR severity. Prevention of IMR by prophylactic ring annuloplasty does not influence remodeling. Ischemic mitral regurgitation is a consequence, not a cause, of postinfarction remodeling; infarct expansion is the more important therapeutic target. (J Am Coll Cardiol 2004;43:377–83) © 2004 by the American College of Cardiology Foundation

Myocardial infarctions (MIs) often initiate a remodeling process that leads to gross ventricular distortion, contractile dysfunction of normally perfused myocardium, symptomatic congestive heart failure (CHF), and premature death (1,2).

Depending on size, location, and transmurality of the infarct, the remodeling process may be associated with the development of ischemic mitral regurgitation (IMR) (1–5). Mild degrees of mitral regurgitation after acute MI portend a substantially increased risk of cardiovascular mortality within five years, even in patients who do not initially have signs of overt CHF (6).

Increasing awareness of the poor prognosis associated with IMR has stimulated much debate regarding the best treatment for these patients. Valve replacement or (preferably) valve repair are being increasingly recommended even for moderate IMR, especially when coronary bypass grafting is indicated. However, careful assessment of the most recent and thoroughly analyzed surgical series leads to the conclusion that surgical intervention for IMR provides little benefit compared to medical therapy for CHF (4,7). The results are predictable and sobering: a steady, almost linear loss of patients, culminating in a five-year survival of 50% (4,7,8).

These clinical results suggest that IMR is a consequence of postinfarction remodeling and does not itself contribute to the progression of the phenomenon. Early infarct expansion is associated with the development of progressive ventricular dilation (1,9), a myopathic process in normally perfused myocardium (10,11), and poor long-term prognosis (1). We therefore hypothesized that infarct expansion is

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the major stimulus for adverse remodeling and greatly outweighs any contribution from gradually progressive mitral valve incompetence.

We tested the hypothesis using a well-established sheep model of chronic IMR in which the development of IMR was prevented by prophylactic ring annuloplasty in one group of animals and infarct expansion was minimized by ventricular restraint in another.

METHODS

Surgical protocol. Twenty-two Dorset male hybrid sheep (Animal Biotech Industries, Doylestown, Pennsylvania) weighing 35 to 40 kg were used for this study. Animals were treated under an experimental protocol approved by the University of Pennsylvania’s Institutional Animal Care and Use Committee (IACUC) and in compliance with NIH publication No. 85-23 as revised in 1985.

Animals were induced with thiopental sodium (10 to 15 mg/kg intravenously [IV]) and intubated. Anesthesia was maintained with isoflurane (1.5% to 2%) and oxygen. All animals received glycopyrrolate (0.4 mg IV) and enrofloxin (10 mg/kg IV) on induction.

Under aseptic conditions, all animals underwent left thoracotomy. Polypropylene snares were loosely placed around the second and third obtuse marginal branches of the circumflex artery supplying the posterolateral LV wall (12). Group assignment was random. Ten animals (control group) underwent closure of the thoracotomy and recovery. Five animals (annuloplasty group) underwent placement of a 24-mm mitral annuloplasty ring (Carpentier-Edwards Physio, Edwards Life Science, Irvine, California) using a 24-mm mitral annuloplasty ring (Carpentier-Edwards Physio, Edwards Life Science, Irvine, California) using standard cardiac surgical techniques. Following termination and at 30 min and two, five, and eight weeks after infarction (1)

Baseline data and infarction. Fourteen days after initial instrumentation, sheep were again anesthetized. The surface electrocardiogram (ECG) and arterial blood pressure were continuously monitored. A high-fidelity pressure transducer (SPC-350, Millar Instruments Inc., Houston, Texas) was inserted via a femoral artery into the left ventricle (LV) for continuous pressure (LVP) monitoring (78534c monitor, Hewlett-Packard, Palo Alto, California). A pulmonary artery catheter (131-h, 7fr, Baxter Healthcare Corp, Deerfield, Illinois) was placed; thermodilution cardiac output was measured in triplicate at each time point for each animal. Animals were disconnected from the ventilator and atrially paced at 120 beats/min for all measurements and echocardiograms.

After baseline hemodynamic and echocardiographic data were recorded, the subcutaneous snares were exposed, tightened, and tied to produce infarction. Each animal received magnesium sulfate (1 g IV), bretylum (10 mg/kg IV), and lidocaine (3 mg/kg IV bolus, then 2 mg/min infusion) before infarction. Hemodynamic and echocardiographic data were collected 30 min after infarction.

Echocardiography. Quantitative two-dimensional subdiaphragmatic echocardiograms were obtained before infarction and at 30 min and 2, 5, and 8 weeks after infarction (1)

Follow-up studies. Hemodynamic and echocardiographic data were collected at 30 min and two, five, and eight weeks after infarction. Following the eight-week study, the animals were euthanized (80 mEq potassium chloride IV bolus). The heart was excised and photographed to confirm infarction size and location.
Table 1. Hemodynamic Data

<table>
<thead>
<tr>
<th></th>
<th>SBP (mm Hg)</th>
<th>LVEDP (mm Hg)</th>
<th>CVP (cm H2O)</th>
<th>CO (l/min)</th>
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<tbody>
<tr>
<td>Control</td>
<td></td>
<td></td>
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<tr>
<td>Pre-infarction</td>
<td>106.2 ± 12.1</td>
<td>5.0 ± 4.0</td>
<td>12.1 ± 4.7</td>
<td>3.5 ± 1.1</td>
</tr>
<tr>
<td>Postinfarction</td>
<td>97.9 ± 15.2</td>
<td>7.5 ± 5.7</td>
<td>12.7 ± 9.5</td>
<td>3.9 ± 1.2</td>
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<tr>
<td>2 weeks</td>
<td>106.1 ± 15.7</td>
<td>5.6 ± 2.1</td>
<td>12.6 ± 5.0</td>
<td>3.7 ± 0.7</td>
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<tr>
<td>5 weeks</td>
<td>102.6 ± 17.7</td>
<td>6.6 ± 1.4</td>
<td>10.8 ± 4.4</td>
<td>3.7 ± 1.0</td>
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<tr>
<td>8 weeks</td>
<td>106.0 ± 19.6</td>
<td>5.0 ± 1.3</td>
<td>11.0 ± 4.3</td>
<td>3.7 ± 0.9</td>
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<tr>
<td>Annuoplasty</td>
<td></td>
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<tr>
<td>Pre-infarction</td>
<td>101.4 ± 30.0</td>
<td>6.0 ± 6.3</td>
<td>13.6 ± 6.8</td>
<td>3.7 ± 1.3</td>
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<tr>
<td>Postinfarction</td>
<td>97.4 ± 15.8</td>
<td>6.0 ± 4.6</td>
<td>11.0 ± 5.1</td>
<td>3.3 ± 1.0</td>
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<tr>
<td>2 weeks</td>
<td>88.8 ± 5.1</td>
<td>6.2 ± 9.0</td>
<td>12.0 ± 8.6</td>
<td>2.8 ± 1.4</td>
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<tr>
<td>5 weeks</td>
<td>95.2 ± 9.5</td>
<td>7.0 ± 1.9</td>
<td>10.0 ± 1.4</td>
<td>3.4 ± 1.0</td>
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<tr>
<td>8 weeks</td>
<td>99.2 ± 11.7</td>
<td>6.2 ± 2.3</td>
<td>14.6 ± 5.0</td>
<td>3.2 ± 1.3</td>
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<tr>
<td>Mesh wrap</td>
<td></td>
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<tr>
<td>Pre-infarction</td>
<td>99.1 ± 19.8</td>
<td>4.3 ± 3.2</td>
<td>12.3 ± 2.5</td>
<td>3.1 ± 0.6</td>
</tr>
<tr>
<td>Postinfarction</td>
<td>96.7 ± 7.0</td>
<td>7.4 ± 6.2</td>
<td>13.9 ± 3.7</td>
<td>3.6 ± 0.8</td>
</tr>
<tr>
<td>2 weeks</td>
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<tr>
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<td>3.3 ± 0.7</td>
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CO = cardiac output; CVP = central venous pressure; LVEDP = left ventricular end-diastolic pressure; SBP = systolic blood pressure.

Statistics. Measurements are reported as means ± standard error of the mean. Between-group differences in all continuous dependent variables (all but MR grade) are compared by analysis of variance for repeated measures. If analysis of variance (ANOVA) revealed significant differences, Student’s t test with the Bonferroni correction was used to assess differences between groups at specific time points post infarction (SPSS, Chicago, Illinois). For each significantly different dependent variable a maximum of six Bonferroni-corrected t tests were performed at a given time point. Differences in the degree of mitral regurgitation between groups were assessed using the nonparametric Kruskal-Wallis test. To evaluate the differences in MR between any two groups at specific time points the Mann-Whitney test with the Bonferroni correction was used. Statistical significance was established at p < 0.05.

RESULTS

Hemodynamic data. No significant differences in LVEDP, central venous pressure, pulmonary artery diastolic pressure, mean arterial pressure, or cardiac output were observed between groups at any of the time points studied (Table 1).

Echocardiographic data. Echocardiographic data are summarized in Table 1. As expected, the control group developed progressive and severe MR (3.4 ± 0.3) during the study period. The MR in the control group was significantly more than in either the annuloplasty (0.6 ± 0.4) or the wrap (1.2 ± 0.3) groups. There was no significant difference in MR between the annuloplasty and wrap groups at any individual time point (Fig. 1).

Normalized LVESV at eight weeks was not altered by prophylactic annuloplasty (2.05 ± 0.29) when compared with controls (2.22 ± 0.21). By ANOVA, considering all experimental time points, the wrap group was significantly different from both the control and annuloplasty groups with respect to LVESV (Fig. 2). Specifically, at eight weeks, LVESV in the wrap group (1.48 ± 0.25) was significantly reduced when compared with the control group. Changes in normalized LVEDV followed a similar pattern (Table 2), though between-group comparisons did not reach statistical significance.

End-systolic muscle-to-cavity-area ratio was preserved in the wrap group, but decreased significantly in both the annuloplasty and control groups; there was a significant difference in the wrap group ESMCAR (1.63 ± 0.14) at eight weeks when compared with both the annuloplasty (1.09 ± 0.17) and control (1.15 ± 0.12) groups (Fig. 3). The circumferential length of the akinetic segment of
myocardium at the high papillary muscle level (WMA) was significantly reduced immediately after infarction in the wrap group (2.9 ± 0.3 cm) when compared to both the annuloplasty (4.1 ± 0.4 cm) and control (4.5 ± 0.4 cm) groups (Fig. 4), indicating that the wrap was effective in reducing early infarct expansion.

Ejection fraction was preserved in the wrap group (Fig. 5). By ANOVA, considering all experimental time points, the wrap group was significantly different from both the annuloplasty and the control groups. The annuloplasty group EF was significantly worse in the annuloplasty group at eight weeks (25.3 ± 2.9%) compared to the wrap group (36.5 ± 2.4%).

**DISCUSSION**

Ring annuloplasty was highly effective in preventing the development of IMR in this established ovine model; however, it had no demonstrable effect on postinfarction ventricular remodeling. In contrast, ventricular wrapping...
reduced acute infarct expansion, preserved EF, and significantly improved measured parameters of postinfarction remodeling. Additionally, ventricular wrapping was as effective as ring annuloplasty in preventing the development of IMR.

A potential limitation of this study was the fact that only the ring annuloplasty group had open-heart surgery and the associated need for a period of aortic cross-clamping with protected global ischemia. We were meticulously attentive with regard to myocardial protection during these procedures. The fact that there was no statistical difference in the preinfarction EF between groups indicates that intraoperative myocardial protection was adequate.

Clinically, IMR occurs most commonly after moderately sized posterolateral infarctions involving the posterior papillary muscle (4,5,17). The degree of mitral regurgitation is typically small initially but increases, often to severe levels, over a varying time course. The model of IMR used in this experiment faithfully replicates the human disease.

Recent laboratory (10,18) and clinical studies (11) have shown that expansion (stretching) of a transmural MI initiates a progressive myopathic process in normally perfused myocardium. This phenomenon is initially localized to myocardium immediately adjacent to the infarct, but extends during the remodeling process to convert contiguous normally perfused myocardium.

Figure 3. End-systolic muscle-to-cavity-area ratio (ESMCAR) in control group (squares), annuloplasty group (circles), and ventricular wrap group (triangles). The ESMCAR did not change during postinfarction remodeling in the wrap group. By analysis of variance, considering all experimental time points, ESMCAR was significantly reduced in both the annuloplasty and control groups when compared with the wrap group. There was no significant difference between the control and annuloplasty groups.

Figure 4. Length of the circumferential wall motion abnormality at the high papillary muscle level (WMA) in control group (squares), annuloplasty group (circles), and ventricular wrap group (triangles). By analysis of variance, considering all experimental time points, the WMA was significantly greater in the annuloplasty and control groups when compared to the wrap group. There was no statistical difference between the control and annuloplasty groups.
myocardium into hypocontractile remodeled myocardium. The stretch-induced myopathic process has been associated with myocyte apoptosis (14) and disruption of the extracellular matrix secondary to activation of matrix metalloproteinases (19). The failure of surgical reshaping operations to improve survival in ischemic cardiomyopathy patients (20–22) strongly suggests that infarct-induced myopathy is very difficult to reverse once established.

Using contrast echocardiography, Jackson et al. (23) has demonstrated that early postinfarction geometric changes consistent with increased regional wall stress occur in the borderzone region adjacent to infarcts undergoing early expansion and subsequent remodeling. A finite-element analysis by Guccione et al. (18) confirms these findings and also demonstrates that once the myopathic process is fully developed, contractile function in nonischemic myocardium is impaired beyond what would be expected from changes in LV geometry and stress distribution. Therefore, early after-infarction loss of contractility is due to mechanical factors; as remodeling progresses the geometric contribution (stress) to myocardial dysfunction is likely outstripped by the myopathic phenomenon that it initiates in normally perfused myocardium. It is for this reason that most operations for established heart failure are ineffective. The salutary effect of ventricular wrapping demonstrated in this study is likely due to its ability to attenuate early infarct expansion, thereby reducing adverse remodeling.

Elimination of moderate to severe ischemic mitral regurgitation, either by valve replacement or valve repair, is an increasingly recommended treatment for patients with symptomatic CHF (4,7). This trend has been driven by improvements in mitral valvuloplasty techniques and reduced perioperative mortality in patients with depressed LV function undergoing open-heart surgery. Recent large clinical studies, however, fail to demonstrate that addressing chronic IMR adds to patient survival beyond what would be expected from optimal medical management (4,7,8,24).

The primary intent of this study was to assess the relative contribution of infarct expansion and mitral regurgitation to remodeling after posterior infarctions that are predisposed to the development of progressive IMR. Our findings indicate that although chronic IMR is a manifestation of postinfarction LV remodeling it contributes minimally to perpetuating the phenomenon of progressive LV dilation. On the contrary, ventricular restraint that prevents infarct expansion dramatically influences the outcome of remodeling and secondarily prevents the development of MR.

The preemptive and prophylactic surgical interventions used in this study cannot, obviously, be directly applied clinically. They represent the best-case scenario of two very different therapeutic strategies. The results of the study do, however, have important clinical implications. Our findings indicate that relief (or prevention) of IMR has very little impact on remodeling. This helps to explain the negligible effect of mitral valve replacement or repair on survival in patients with IMR. This study confirms the results of earlier experiments in our laboratory (13,25), and in doing so reinforces the thesis that therapies that minimize infarct expansion early after acute MI are more likely to limit adverse postinfarction remodeling and thereby improve survival.

The threshold for surgical treatment of mitral regurgitation caused by primary valvular disease is declining because of improved repair techniques, reduced operative mortality, and proven benefits in reducing the incidence of irreversible LV dysfunction. Our data would caution against extrapolating these results to patients with IMR. In IMR, mitral regurgitation is a consequence rather than a cause of
postinfarction left ventricular remodeling. As these data support, the primary therapeutic target is early infarct expansion, not late mitral regurgitation.

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