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Elimination of Ischemic Mitral Regurgitation Does Not Alter Long-Term Left Ventricular Remodeling in the Ovine Model

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Abstract

Background—The efficacy of annuloplasty for ischemic mitral regurgitation (IMR) has been difficult to establish. Using an established ovine model of IMR, we tested the ability of ring annuloplasty to durably relieve IMR and reverse or limit progression of left ventricular (LV) remodeling during a clinically relevant follow-up period.

Methods—A posterolateral infarction known to result in chronic IMR was initiated in 33 sheep. Echocardiography was used to assess LV end diastolic and systolic volumes and IMR (0 to 4 scale) before and 8 weeks after infarction. Eight weeks after infarction, 20 surviving animals with $\geq 2+$ IMR were randomized (1:1) to no treatment or undersized, semi-rigid, complete ring annuloplasty placement. LV remodeling and IMR were assessed at 4 and 6 months after infarction.

Results—All animals had similarly sized LV volumes at baseline (end systolic, 27.8 ± 4.6 mL; end diastolic, 53.5 ± 6.4 mL). The 20 randomized animals survived to complete the study. The degree of IMR before randomization was similar in treatment (2.6 ± 0.4) and control (2.8 ± 0.3) groups. At the 6-month follow-up, the degree of IMR was significantly less in the annuloplasty group (0.3 ± 0.1 vs 3.4 ± 0.6); however, LV volumes in the treatment group were not significantly different from the control group (end systolic, 82.1 ± 15.6 vs 81.1 ± 8.6 mL; end diastolic, 110.4 ± 22.1 vs 111.1 ± 16.5 mL).

Conclusions—In a clinically relevant ovine model of IMR, annuloplasty provides durable relief from IMR during an extended follow-up period but does not significantly influence LV remodeling.

Ischemic mitral regurgitation (IMR) occurs when a structurally normal mitral valve is rendered incompetent as a result of myocardial infarction (MI)-induced left ventricular (LV) remodeling [1]. IMR is present in some degree in 1.6 to 2.8 million patients in the United States [2] and in nearly 50% of patients with reduced LV ejection fraction (LVEF; <0.40) who undergo coronary artery bypass grafting [3]. The magnitude of this clinical problem is large and expected to grow substantially during the next 2 decades as the population ages [3].

Ischemic mitral regurgitation increases mortality even when mild, with a strong, graded relationship between severity and reduced survival [2,4]. Although mitral valve repair with ring annuloplasty, typically performed in conjunction with coronary revascularization, has

become the preferred treatment [5], it has been difficult to definitively establish that such procedures consistently lead to significant reverse LV remodeling or prolong survival relative to medical therapy and revascularization alone [6–8]. Surgical efficacy has been particularly difficult to demonstrate in patients with severely dilated ventricles and IMR of moderate severity [9]. Previous experimental work in our laboratory suggests that IMR may be a manifestation of the remodeling process after MI rather than a significant contributor to progressive LV dilatation and loss of global function [10].

The optimal therapeutic approach to IMR remains to be definitively established, and randomized prospective clinical studies are badly needed. The available clinical data are confounded by their retrospective nature, small sample size, patient selection bias, high incidence of recurrent IMR, variable infarct properties, lack of control groups, and the almost universal use concomitant coronary revascularization [6,7,10–12].

To help better establish the place of mitral valve repair in the treatment armamentarium for heart failure, we designed a laboratory experiment intended to control for the common clinical confounding factors of concomitant revascularization, variable infarct size and location, and importantly, recurrent IMR. We studied the effect of surgical correction of established IMR on postinfarction LV remodeling in the severely dilated ovine posterobasal infarct model during an extended period after MI (6 months) using quantitative 3-dimensional echocardiography.

Material and Methods

The study protocol was reviewed and approved by the University of Pennsylvania School of Medicine Institutional Animal Care and Use Committee and was in compliance with *Guide for the Care and Use of Laboratory Animals* (US National Institutes of Health publication No. 85-23, National Academy Press, Washington, DC, revised 1996).

Surgical Protocol

A schematic presentation of the experimental design is presented in Figure 1. Thirty-three adult male sheep (weighing 35 to 40 kg) were pretreated with buprenorphine (2 µg/kg) and then sedated with sodium thiopental (10 to 15 mg/kg intravenously [IV]), intubated, and anesthetized with isoflurane (1.5% to 2.0%) and oxygen. All animals also received glycopyrrolate (0.02 mg/kg IV) and cefazolin (1.0 grams IV). The electrocardiogram, arterial blood pressure, and pulmonary artery pressure were monitored throughout the procedure.

Under sterile conditions, all animals underwent right thoracotomy to allow ligation of all distal branches of the left circumflex coronary artery between the lateral cardiac vein and the middle cardiac vein (Fig 2A). Permanent occlusion of these arteries reliably results in a transmural posterobasal MI that involves approximately 20% of the LV mass and typically includes the entire posterior papillary muscle [10,13]. Animals received magnesium sulfate (1 grams IV), amiodarone (90 mg IV infusion over 1 hour), and lidocaine (3 mg/kg IV bolus, then 2 mg/min infusion) before MI. After hemodynamic and electrophysiologic stabilization, the incision was then closed and the animal permitted to recover.

At 8 weeks after MI, anesthesia was again induced as described in surviving animals, and chest wall echocardiography was used to assess the degree of IMR. Animals with less than 2+ IMR were euthanized and excluded from further analysis. All remaining animals (those with ≥2 IMR) were randomized to the untreated control group or underwent surgical placement of a size 24 mitral annuloplasty ring (Carpentier-Edwards Physio annuloplasty, Edwards Life Science, Irvine, CA). Valve repair was performed through a left thoracotomy

using standard cardiac surgical techniques. Quantitative 3-dimensional echocardiography (3DE) was performed before cardiopulmonary bypass to assess LV volumes. After termination of cardiopulmonary bypass and decannulation, animals underwent repeat 3DE to assess for residual IMR, followed by closure of the thoracotomy and recovery from anesthesia.

Animals randomized to the control group underwent a small midline laparotomy to allow transdiaphragmatic quantitative 3DE to be performed. Chest wall echocardiography in sheep provides adequate viewing windows to reliably assess the degree of IMR but does not permit sufficient viewing windows to allow assessment of LV volumes.

Echocardiographic Protocol

Real-time 3DE was performed before coronary artery ligation as well as at 8 weeks (ie, just before randomization), 16 weeks, and 24 weeks after MI in all sheep. Echocardiography was also performed after separation from cardiopulmonary bypass in animals randomized to valve repair. All echocardiograms were recorded using a Philips iE 33 platform with a 7-MHz ultrasound probe (Philips, Bothell, WA). Full volume 3D data were acquired. These data sets were exported for offline analysis using QLAB software (Philips). The 3D image was manipulated to display 2 orthogonally related long-axis views, bisecting each other on the central long axis of the LV.

End diastole (ED) was defined as the frame before closure of the mitral valve and end systole (ES) as the frame before closure of the aortic valve. LV volumes (LVEDV and LVESV) were obtained for each according to the software manufacturer's recommended method. Briefly, the basal and apical limits of the LV are defined by manually placing reference points on the image. The software then defines the interface between the endocardium and LV cavity, and thus the LV envelope, by inserting splines to connect with the manually inserted reference points. This is repeated for each long-axis view at both ED and ES. The 3D image may then be rotated about its long axis, and the line defining the endocardial envelope of the LV may be manually fine-tuned to correct for interpolation error. The LVEDV and LVESV are then computed, from which the LVEF may be calculated. LVEDV and LVESV are reported as raw volumes and are also normalized to pre-MI values.

The degree of MR was determined quantitatively by assessing the area of the regurgitant jet as a percentage of left atrial area in the apical 4-chamber view. The following grading scale was used: grade 0, no MR; grade 1 less than 20%; grade 2, 20% to 40%; grade 3, 40% to 60%; and grade 4, more than 60% [14].

Hemodynamic Measurements

The surface electrocardiogram and arterial blood pressure were continuously monitored (Sonometrics Inc, London, ON, Canada) and recorded during all data collection procedures. A high-fidelity pressure transducer (SPC-350, Millar Instruments Inc, Houston, Texas) was inserted through a femoral artery into the LV for continuous pressure (LVP) monitoring (78534c monitor, Hewlett-Packard, Palo Alto, CA). A pulmonary artery catheter (131-h, 7F, Baxter Healthcare Corp, Deerfield, IL) was placed; thermodilution cardiac output was measured in triplicate at each time point for each animal.

Follow-Up Studies

At 16 and 24 weeks after MI (8 and 16 weeks after repair in the annuloplasty group), surviving sheep were anesthetized as described and underwent transdiaphragmatic

quantitative 3DE to assess LVEDV, LVESV, LVEF, and degree of IMR. Hemodynamic data were also collected.

After data collection was completed at 24 weeks, animals were euthanized with an overdose of potassium chloride and the heart was excised. The right ventricle and atria were removed from the specimen, and the LV was opened through the intraventricular septum. A digital photograph of the opened LV was taken, and the infarct location was verified (Fig 2B). All photographs were imported into an image analysis program (Image Pro Plus, MediaCybernetics; Silver Spring, MD), and computer-assisted planimetry was performed on the photographic image to quantify the infarct size as a percentage of the LV.

Statistical Analysis

Measurements are reported as means $\pm$ standard deviations. Between-group differences in all continuous dependent variables (all but MR grade) were compared by analysis of variance for repeated measures. If analysis of variance revealed significant differences, a *t* test with the Bonferroni correction was used to assess differences between groups at specific time points after MI using SPSS software (SPSS, Chicago, IL). Differences in the degree of MR 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

Animal Survival and MR

Seven animals died of arrhythmia or heart failure within the first 2 weeks after infarction, before the 8-week post-MI randomization. Six animals had less than 2+ IMR at the 8-week post-MI echocardiographic studies and were removed from the study and euthanized. The 20 remaining animals were randomized equally to the control group (MR, 2.8 ± 0.3) or treatment group (MR, 2.6 ± 0.4). In the control group, the degree of MR at 16 weeks and 24 weeks after MI was 3.1 ± 0.6 ($p = 0.3$ vs 8 weeks after MI) and 3.4 ± 0.8 ($p = 0.1$ vs 8 weeks after MI), respectively. In the treatment group, MR was 0 ± 0 immediately after annuloplasty placement and 0.4 ± 0.1 and 0.3 ± 0.1 at 16 and 24 weeks after MI, respectively.

Hemodynamic Data

No significant differences in LVED pressure, central venous pressure, mean arterial pressure, or cardiac output were observed between groups at any of the time points studied. The diastolic pulmonary artery pressure was significantly lower in the annuloplasty group (16.5 ± 1.6 vs 21.8 ± 1.4 mm Hg, $p = 0.04$; Table 1).

Echocardiographic Data

Echocardiographic data are presented in Table 2 and summarized in Figure 3. All animals in both groups experienced extensive LV remodeling by 8 weeks post-MI. In the control group, LVESV increased from 27.3 ± 5.4 mL before MI to 55.5 ± 5.7 mL at 8 weeks; in the annuloplasty group, LVESV increased from 28.2 ± 3.5 to 53.2 ± 5.3 mL during the same period. Similar changes occurred in LVEDV (Table 2). LVEF decreased to a similar extent in both groups 8 weeks after MI (0.482 ± 0.055 to 0.308 ± 0.032 in controls and 0.483 ± 0.041 to 0.328 ± 0.110 in the annuloplasty group). LV volumes increased progressively in both groups at 16 and 24 weeks (Table 2; Fig 3). At 24 weeks after MI, the LVESV had increased in the control group by a factor of 3.1 ± 0.7 relative to baseline and had increased in the annuloplasty group by a factor of 3.3 ± 0.5 . At 24 weeks after MI, LVEDV had

increased 2.2 ± 0.5 relative to baseline in the control group and 2.1 ± 0.5 in the annuloplasty group, and the LVEF was $0.26.1 \pm 0.043$ in the control group and 0.254 ± 0.011 in the annuloplasty group.

Postmortem assessment demonstrated that the infarct size as a percentage of the LV was similar in the control group ($21.7\% \pm 5.4\%$) and in the annuloplasty group ($22.6\% \pm 4.7\%$), indicating that the remodeling stimulus was the same in both groups (Fig 2C).

Comment

Laboratory [15,16] and clinical studies [17] have shown that expansion (stretching) of a MI initiates a progressive myopathic process in normally perfused myocardium. This phenomenon is initially localized to myocardium immediately adjacent to the infarct, but extends over time to convert contiguous normally perfused myocardium into hypocontractile remodeled myocardium. Myocyte apoptosis [18] and disruption of the extracellular matrix secondary to activation of matrix metalloproteinases [19] have been shown to contribute to loss of contractile function in perfused myocardial segments outside the infarct region. The end result of this ventricular remodeling process is a globally dilated poorly functioning ventricle. Depending on the size, location, and transmural extent of the infarct, LV remodeling can be associated with discrete anatomic lesions such as LV aneurysm and IMR.

The incidence of IMR is rising, and its presence even when mild, is associated with poor clinical outcomes [2–4]. Many clinical approaches to IMR have been advocated; however, the optimal treatment has yet to be established.

In this experiment using an ovine model, we demonstrated that relief from established moderate IMR in the context of a severely dilated LV does not, to any significant extent, alter subsequent LV remodeling. This study builds on our prior work with the same animal model in which we placed annuloplasty before MI to prevent the development of IMR and demonstrated that remodeling was not appreciably improved relative to untreated controls [10]. The results of these two laboratory studies indicate that it is possible, in at least some cases, for IMR to be solely a manifestation of the post-MI remodeling process rather than a contributor to ongoing LV dilatation and functional loss.

The current study was designed to maximize the clinical relevance and importance of the experiment. We implemented complete ring annuloplasty, an accepted surgical therapy for IMR, in a model of severe LV remodeling and moderate MR, with all animals being monitored for an extended period of time (4 months) after randomization with advanced 3DE tools to quantitatively assess the degree of ventricular remodeling. The ovine model provides freedom from important confounding variables such as untreated myocardial ischemia, recurrent MR, and inconsistent infarct characteristics that are difficult to control for in clinical studies. The results of this study lead to the sobering conclusion that, at least in the case of a severely dilated LV, relief from moderate IMR has little effect on global LV remodeling to reverse it or to prevent its progression. Although our experimental findings and related conclusions may seem counterintuitive, there is a growing body of clinical data to support them.

Elimination of moderate to severe IMR by valve replacement or valve repair is an increasingly recommended treatment for patients with symptomatic heart failure. This trend has been driven by increased surgeon familiarity with valvuloplasty techniques and reduced perioperative death in patients with severely depressed LV function undergoing open heart procedures [20]. No randomized, controlled, prospective clinical data are available to assess the efficacy of mitral valve repair in improving longevity in patients with IMR; however, this important issue has been addressed by several recent, well-conceived, retrospective

studies that used propensity analysis to develop control groups matched for key demographic and clinical factors. These studies have not demonstrated a definitive survival benefit associated with mitral valve repair for IMR [6,7,11,12,20–22].

Assessing the clinical effect of annuloplasty for IMR on LV remodeling has been even more difficult than determining its effect on longevity, because long-term quantitative echocardiographic data in these patients has been infrequently reported. Recently, several small cohorts of IMR patients treated with undersized annuloplasty have been reported in which midterm follow-up LV dimension or volume data are available [8,9]. Although these studies are uncontrolled and most of the patients had concomitant coronary revascularization, the reported data are illustrative. These studies have characteristically demonstrated a bimodal LV remodeling response to annuloplasty. Mild to moderate reverse remodeling is achieved in patients with smaller preoperative LV volumes and greater degrees of IMR, with little or no reverse remodeling occurring in very large ventricles with associated moderate IMR.

The available laboratory and clinical data support the conclusion that in a significant fraction (possibly most) of IMR patients, MR is primarily a manifestation of infarct-induced LV remodeling rather than a significant contributor to the process. The relative contribution of IMR and the infarct itself to the remodeling process likely varies substantially between patients, suggesting that a better understanding of the relative contribution of each factor in individual patients will be required to develop a patient-specific approach to therapy and improved clinical results.

Regardless of whether IMR contributes significantly to ongoing remodeling in an individual patient, it is always a relatively late and maladaptive manifestation of the remodeling process; therefore, interventions designed to treat IMR will always be, at best, palliative in nature. Therapeutic approaches designed to limit early infarct expansion may in the long run obviate the need for late post-MI interventions such as mitral valve repair in the chronically remodeled heart [22,23].

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Fig 1.

Flow chart showing the experimental protocol. (IMR = ischemic mitral regurgitation; MI = myocardial infarction.)

Fig 2.

Infarct characteristics. (A) Posterior view of an ovine heart as viewed through a right thoracotomy. All branches of the circumflex coronary artery that cross the lateral margin of the left ventricle (LV) and supply the posterobasal wall between the lateral cardiac vein and the middle cardiac vein are ligated (RV = right ventricle.) (B) View of the ovine left ventricle open through the intraventricular septum 24 weeks after the posterobasal myocardial infarction depicted in Panel A. The infarct involves most of the posterior left ventricular wall and the entire posterior papillary muscle. (C) Infarct size as determined by postmortem planimetry in control and annuloplasty groups. Error bars represent standard deviations.

Fig 3.

Echocardiographic data for annuloplasty group (dashed line) and control group (solid line): (A) Serial left ventricular (LV) end systolic volume normalized to preinfarction value. Annuloplasty was placed 8 weeks after myocardial infarction (MI) in the annuloplasty group. The control group received no treatment. (B) Serial left ventricular end diastolic volume normalized to preinfarction value. (C) Serial ejection fraction (EF). (D) Degree of mitral regurgitation (MR) on standard 0 to 4 scale. The only statistically significant difference between groups was the degree of mitral regurgitation at 16 and 24 weeks after myocardial infarction. Error bars represent standard deviations.

Table 1

Hemodynamic Data

Group	Heart rate (beats/min)	SBP (mm Hg)	DPAP (mm Hg)	LVEDP (mm Hg)	CVP (cm H ₂ O)	CO (L/min)
Controls						
Before MI	104.6 ± 8.2	106.3 ± 14.1	14.5 ± 1.3	6.2 ± 2.4	11.3 ± 1.6	4.1 ± 0.7
After MI						
8 wks	100.4 ± 16.7	106.1 ± 15.7	19.6 ± 2.3 ^a	5.8 ± 3.6	12.6 ± 5.0	3.8 ± 0.7
16 wks	105.7 ± 11.7	102.6 ± 17.7	18.0 ± 2.8	9.6 ± 4.4	10.8 ± 4.4	3.7 ± 1.0
24 wks	113.7 ± 18.7	106.0 ± 19.6	21.8 ± 1.4 ^a	11.0 ± 5.3 ^a	11.0 ± 4.3	3.2 ± 0.9 ^a
Annuloplasty						
Before MI	100.0 ± 9.9	108.4 ± 6.4	13.3 ± 1.9	6.0 ± 6.3	13.36 ± 6.8	4.2 ± 0.7
After MI						
8 wks	97.8 ± 7.7	104.4 ± 8.4	18.1 ± 3.0 ^a	6.2 ± 9.0	12.0 ± 8.6	3.9 ± 0.4
16 wks	100.5 ± 8.9	95.2 ± 9.5	16.1 ± 1.0 ^a	9.0 ± 3.3	10.0 ± 1.4	3.4 ± 1.0
24 wks	103.7 ± 9.7	107.4 ± 11.4	16.5 ± 1.6 ^{a,b}	12.9 ± 5.3 ^a	14.6 ± 5.0	3.1 ± 1.3 ^a

^a $p < 0.05$ vs before MI.^b $p < 0.05$ vs control group.

CO = cardiac output; CVP = central venous pressure; DPAP = diastolic pulmonary artery pressure; LVEDP = left ventricular end diastolic pressure; MI = myocardial infarction; SBP = systolic blood pressure.

Table 2

Echocardiographic Data

Group	MR (0-4)	LVESV (mL)	LVEDV (mL)	Norm LVESV	Norm LVEDV	EF (%)
Control						
Before MI	0.3 ± 0.2	27.3 ± 5.4	52.4 ± 6.7	1.0 ± 0.0	1.0 ± 0.0	48.2 ± 5.5
After MI						
8 wks	2.8 ± 0.3	55.5 ± 5.7 ^a	80.4 ± 9.3 ^a	2.1 ± 0.6 ^a	1.6 ± 0.3 ^a	30.8 ± 3.2 ^a
16 wk	3.1 ± 0.6	73.1 ± 6.4 ^{a,b}	99.0 ± 6.8 ^{a,b}	2.8 ± 0.7 ^{a,b}	1.9 ± 0.3 ^{a,b}	26.2 ± 3.6 ^{a,b}
24 wks	3.4 ± 0.8	81.1 ± 8.6 ^{a,b}	111.1 ± 16.5 ^{a,b}	3.1 ± 0.7 ^{a,b}	2.2 ± 0.5 ^{a,b}	26.1 ± 10.4 ^a
Annuloplasty						
Before MI	0.2 ± 0.2	28.2 ± 3.5	54.6 ± 6.1	1.0 ± 0.0	1.0 ± 0.0	48.3 ± 4.1
After MI						
8 wks	2.6 ± 0.4	53.2 ± 5.3 ^a	80.4 ± 10.6 ^a	2.0 ± 0.4 ^a	1.5 ± 0.2 ^a	32.8 ± 11.0 ^a
16 wks	0.4 ± 0.1 ^{b,c}	76.7 ± 17.6 ^{a,b}	98.9 ± 14.6 ^{a,b}	2.8 ± 0.5 ^{a,b}	1.8 ± 0.2 ^{a,b}	23.0 ± 9.8 ^{a,b}
24 wks	0.3 ± 0.1 ^{b, c}	82.1 ± 15.6 ^{a,b}	110.4 ± 22.1 ^{a,b}	3.3 ± 0.5 ^{a,b}	2.1 ± 0.5 ^{a,b}	25.4 ± 3.9 ^{a,b}

^a Statistically significant difference ($p < 0.05$) from before MI.^b Significant difference from 8 weeks after MI.^c Significant difference from control group.

EF = ejection fraction; LVEDV = left ventricular end diastolic volume; LVESV = left ventricular end systolic volume; MI = myocardial infarction; MR = mitral regurgitation; Norm = normalized to preinfarction.