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Moderate mitral regurgitation accelerates left ventricular remodeling after postero-lateral myocardial infarction

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Abstract

Background—Chronic ischemic mitral regurgitation (CIMR: MR) is associated with poor outcome. However, the effect of CIMR on left ventricular (LV) remodeling after postero-lateral myocardial infarction (MI) remains controversial. We tested the hypothesis that moderate MR accelerates LV remodeling after postero-lateral MI.

Methods/Results—Postero-lateral MI was created in 10 sheep. Cardiac MRI was performed 2 weeks before and 2, 8 and 16 weeks after MI. LV and right ventricular (RV) volumes were measured and regurgitant volume (RegurgVolume) calculated as the difference between LV and RV stroke volumes.

Multivariate mixed effect regression showed that LV volumes at end-diastole (ED) and end-systole (ES) and LV sphericity were strongly correlated with both RegurgVolume ($p < 0.0001$, $p = 0.0086$ and $p = 0.0007$ respectively) and %Infarct area ($p = 0.0156$, $p = 0.0307$, and $p < 0.0001$ respectively). On the other hand, while LV hypertrophy (LV wall volume) increased from 2 to 16 weeks post-MI there was no effect of either RegurgVolume or %Infarct.

Conclusions—Moderate mitral regurgitation accelerates LV remodeling after postero-lateral MI. Further studies are needed to determine whether mitral valve repair is able to slow or reverse MI remodeling after postero-lateral MI.

Keywords

Myocardial Infarction; Mitral Valve; Mitral Regurgitation; Mitral Repair; Remodeling

Introduction

Chronic ischemic mitral regurgitation (CIMR: MR) affects 1.2 to 2.1 million patients in the United States, with more than 400,000 patients having moderate-to-severe MR. [1] These

numbers are expected to progressively increase as the population rapidly ages and more patients survive acute MI. [1] CIMR of 2+ severity discovered at cardiac catheterization for symptomatic coronary artery disease has a 1-year mortality of approximately 17% [2] and the 1-year mortality for 3+ and 4+ CIMR is approximately 40%. [2]

An important unanswered question is whether moderate MR accelerates post-MI LV remodeling. In a provocative experiment Guy et al performed mitral annuloplasty prior to postero-lateral MI in sheep. [3] Surprisingly, they found that prevention of moderate MR did not influence LV remodeling, leading the authors to conclude that “ischemic MR is a consequence, not a cause, of post-infarction remodeling.” [3] The findings of the study by Guy et al are critically important in that they are being used to argue against mitral valve repair in patients with CIMR. [4]

There is evidence to the contrary. Beeri and colleagues simulated MR with an LV to left atrial shunt in sheep after an antero-apical MI. [5, 6] They showed that flow through the shunt increased LV remodeling and simulated mitral repair (closure of the shunt) at 1 month was associated with reverse remodeling such that the LV size at 3 months was similar to that before MI. [5]

However, there are concerns about both of these important studies. Liel-Cohen and colleagues have previously shown that the sheep model of CIMR develops only mild MR (regurgitant fraction of 13%) 8 weeks after postero-lateral MI [7] and mild MR may have been insufficient to show a difference between the prophylactic annuloplasty and control groups in the study by Guy et al [3]. In addition, studies done by Beeri et al used sheep with an antero-apical MI and the shunt was implanted into the LV base. [5, 6] Both of these factors may have altered the natural history of remodeling associated with CIMR.

LV and regurgitant volumes can be accurately measured with cardiac magnetic resonance imaging (MRI). [8, 9] For instance, recent meta-analyses demonstrate that 3D echocardiography underestimates left and right ventricular (RV) volumes when compared with MRI. [10, 11] We used MRI to more accurately measure LV and regurgitant volumes. We tested the hypothesis that moderate MR accelerates LV remodeling after postero-lateral MI in sheep.

Methods

Animals used in this study were treated under a protocol approved by the San Francisco VA Medical Center’s Institutional Animal Care and Use Committee (IACUC) and in compliance with the “Guide for the Care and Use of Laboratory Animals” prepared by the Institute of Laboratory Animal Resources, National Research Council, and published by the National Academy Press, revised 1996.

Myocardial Infarction

Adult sheep underwent postero-lateral MI as previously described. [12] Briefly, castrated male Dorsett sheep were anesthetized and a left 6th intercostal space thoracotomy was made using sterile technique. The pericardium was opened and polypropylene sutures placed around the second and third circumflex marginal coronary arteries. [12] The vessels were ligated, the pericardium was closed, the thoracotomy closed in layers and the sheep recovered from anesthesia.

Magnetic resonance imaging

Two weeks before MI and 2, 8 and 16 weeks after MI, echocardiography and cardiac MRI were performed as previously described. [13] Briefly, sheep were anesthetized and a neck

incision made using sterile technique. The jugular vein and common carotid artery were exposed. Heparin 5000 IU, Atropine 1.0 g, Metoprolol 5mg and Lidocaine (100 mg iv followed by 2 mg/min iv continuous) was administered. 8 Fr vascular introducers were inserted into the jugular vein and carotid artery and non-ferromagnetic transducer tipped pressure catheters (model SPC-320, Millar Instruments, Houston, TX) advanced into the LV and RV using fluoroscopic and echocardiographic guidance. Peak LV pressure maintained at 90 mm Hg with Neosynephrine IV continuous.

A midline sub-xyphoid incision was made. Subdiaphragmatic two-dimensional long axis echocardiographic images were obtained (Acuson Sequoia C256 with a 3V2c (2–3 MHz) probe, Siemens AG, Washington DC) as described by Kelley and colleagues. [14] Echocardiography was used to confirm the position of pressure catheters and the presence of MR but was not quantitatively analyzed.

Each sheep was positioned on its left side in the MRI scanner (Symphony 1.5 Tesla with Quantum gradients, Siemens Medical Systems, Iselin, NJ) with its chest centered under a Helmholtz coil. A series of MRI images in the orthogonal short- and long-axis planes were obtained. MRI data acquisition was triggered when $dLV\text{ pressure}/dt$ reached 10% of the maximum value.

Image Analysis

A customized program (iContours, Liang Ge, Cardiac Biomechanics Lab, San Francisco, CA) based on the medical image processing and visualization environment Mevislab (v 2.1, Mevislab, Bremen, DE) was used to contour the endocardial and epicardial surfaces of the LV and RV (Figure 1). Endocardial and epicardial surfaces were formed using a Delaunay triangulation [15] of contour points in three dimensions. 3D volumes (Volume) of the LV and RV were calculated by piecewise integration of the volume enclosed by the epicardial and endocardial surfaces throughout the cardiac cycle. ED was defined as the first image of the image set (10% maximum $dLV\text{ pressure}/dt$). The image with the smallest volume was defined as end-systole (ES). The stroke volumes of the LV were calculated as:

$$SV_{LV} = \text{Volume}_{LV,ED} - \text{Volume}_{LV,ES} \quad (1)$$

where SV_{LV} is stroke volume. Stroke volume of the RV (SV_{RV}) was calculated in a similar fashion.

The Regurgitant Volume (RegurgVolume) was calculated as the difference between the LV and RV stroke volume:

$$\text{RegurgVolume} = SV_{LV} - SV_{RV} \quad (2)$$

The regurgitant fraction (RegurgFraction) was calculated as:

$$\text{RegurgFraction} = \text{RegurgVolume} / SV_{LV} \quad (3)$$

The epicardial wall of the LV at the end-diastole was also manually contoured and the LV wall volume (WallVolume) was calculated as:

$$\text{WallVolume} = \text{Volume}_{LV,ED,Epi} - \text{Volume}_{LV,ED,Endo} \quad (4)$$

where epi is epicardial and endo is endocardial volume.

Long and short axis diameters were measured on all 6 of the MRI long axis images at end-diastole (Figure 1) and averaged. LV long axis was the distance from the LV apex to the mid point of the mitral valve opening. LV short axis was measured perpendicular to the long axis at the point of largest LV short axis diameter. Sphericity of the LV was calculated as:

$$Sphericity = LV \text{ Short Axis} / LV \text{ Long Axis}$$

Body surface area (BSA) was calculated using the following equation:

$$BSA = 0.084 \text{Weight}^{2/3} \quad (5)$$

where BSA units are m² and Weight is sheep weight in kg. [16]

Post-mortem examination

Sheep were sacrificed one week after the 16 week MRI. The heart was excised. The right ventricle was removed. The LV was opened by incising the septum and the anterior leaflet of the mitral valve. A digital photograph was taken of the LV endocardium. LV and MI areas were determined (ImageJ) and the percent MI area calculated. [17]

Statistical Analysis

All values are expressed as mean $\pm$ standard deviation. The significance level was set at $P < 0.05$.

A multivariate mixed effect analysis (Proc Mixed, SAS version 9.2, SAS Institute Inc., Cary, NC) was performed. A mixed model analysis uses a maximum likelihood or restricted maximum likelihood estimation technique as opposed to ordinary least squares. The following regression model was used::

$$DepVar = RegurgVolume_i + Time + \%MI \quad (6)$$

where the dependent variable, *DepVar*, is either LV, wall volume, short axis, long axis or sphericity indexed to the BSA, *RegurgVolume_i* is RegurgVolume indexed to BSA, *Time* is time after MI and *%MI* is the percent of the LV wall that was infarcted. If the relationship was significantly non-linear, a natural log transformation of the dependent variable was used to make the relationship linear. [18] Individual sheep were included as a random effect. All cross terms were initially included. Terms that were not significant were sequentially eliminated in a backwards fashion. [19] Regression coefficients were standardized by multiplication with group standard deviation.

RegurgVolume was also treated as a dichotomous variable. In that case, a dummy variable, HighLow, was equal to 1 if RegurgVolume Index averaged over the 3 post-MI data points was $> 10 \text{ ml/m}^2$.

Results

Ten sheep underwent standard postero-lateral MI. One sheep died during MI from ventricular arrhythmias. Nine sheep completed the protocol.

Sheep weight is seen in Table 1. Sheep weight remained relatively constant until week 8 but then increased to 67.0 kg at 16 weeks (12.8%; $p < 0.0001$). The average BSA calculated for all sheep and all time points using Equation 5 was 1.26 m^2 . The relationship between end – diastolic LV volume and both weight and BSA were equally significant ($p = 0.00157$ and $p = 0.00133$ respectively). Therefore and as above, cardiac volumes and dimensions were indexed to BSA for statistical analysis.

LV pressure at ED and ES after postero-lateral MI is seen in Table 1. LV pressure at ES was maintained near 90 mm Hg during data collection ($p = \text{NS}$). The LV pressure at ED increased from 5.1 ± 1.5 to 6.9 ± 1.5 mm Hg at 2 weeks but then remained constant ($p = \text{NS}$).

Percent infarct area was $22\% \pm 7\%$.

MR

Development of MR after postero-lateral MI is seen in Table 1. The RegurgVolume and RegurgFraction increased rapidly until 8 weeks ($p = 0.0035$ and $p = 0.0021$ respectively) and then increased more slowly until 16 weeks ($p = \text{NS}$ vs Week 8).

Animals were divided into High (average RegurgVolume index ≥ 10 ; $n = 5$) and Low RegurgVolume index (average RegurgVolume Index < 10 ; $n = 4$) groups. Figure 2 shows the development of RegurgVolume index (A) and RegurgFraction (B) over time in High and Low MR groups.

LV Volume

The change in LV volume after postero-lateral MI is seen in Table 1. Similar to the amount of MR, LV volume at end-diastole and end-systole increased rapidly until 8 weeks ($p = 0.0002$ and $p = 0.0036$ respectively) and then increased more slowly until 16 weeks ($p = \text{NS}$ vs Week 8).

Figure 3 shows the relationship between the change in LV volume index at ED (A) and ES (B) and RegurgVolume index. Briefly, multivariate mixed effect regression (Equation 6) showed that LV volume index at ED and ES were significantly correlated with both RegurgVolume index and %Infarct. Standardized regression coefficients suggest that the effect of RegurgVolume index was the predominant determinant of LV volume at ED. However, the effect of RegurgVolume and %Infarct on LV volume at ES was similar. The results (standardized coefficients and p values) of the linear mixed-effects model regression are seen in Table 2.

As above, data were grouped into High and Low RegurgVolume Index groups. LV volume at ED and ES over time in the two groups is shown in Figure 4.

LV Dimensions, Wall volume and Sphericity

Changes in LV short and long axis diameter, wall thickness, sphericity and LV wall volume after postero-lateral MI are seen in Table 1. LV short and long axis diameters increased by 14.4 and 4.2% respectively at 16 weeks ($p = 0.0022$ and $p = \text{NS}$ respectively). As a consequence, LV sphericity increased by 9.7% at 16 weeks after MI ($p = 0.0253$). Wall thickness actually decreased slightly (-6.3% at 8 weeks and -0.3% at 16 weeks ($p = \text{NS}$)). As a consequence, although LV volume at ED increased, the LV wall volume increased only slightly ($p = 0.0063$).

Multivariate mixed effect regression (Equation 6) showed that LV short axis index, long axis index and sphericity were strongly correlated with both RegurgVolume and %Infarct

area. There was no effect of either RegurgVolume or %Infarct on LV wall volume. As above, p values are seen in Table 2.

Figure 5 shows the change in LV Sphericity at ED (A) and LV wall volume at ED (B) over time in the High and Low MR groups.

Comment

The principal finding of the study was that moderate ischemic MR accelerates LV remodeling after postero-lateral MI in the sheep.

Severity of MR in the sheep model

The American Society of Echocardiography recommendations for evaluation of valvular regurgitation [20] breaks moderate MR into low moderate and high moderate groups. Low moderate is defined as a regurgitant fraction between 30 and 39% and a regurgitant volume between 30 and 44 ml. Assuming that the average adult human BSA equals 1.79 m² [21], RegurgVolume Index for the low moderate group would range from 16.8 to 24.5 ml/m². In our hands, the severity of MR in sheep 16 weeks after postero-lateral MI therefore ranges from mild to low moderate. This is somewhat greater than the amount of MR measured by Liel-Cohen and colleagues in the same animal model. [7] The reason for the difference is unclear but may be related to the greater accuracy of MRI based measurement of MR in the sheep model.

Relationship between regurgitant volume and LV volume

A recent study by Uretsky et al. described for the first time a strong correlation between regurgitant volume and ED volume index ($r^2 = 0.8$) in patients with pure (non-ischemic) MR. [22] Regurgitant volume and ES volume index were also associated although the correlation was not as strong ($r^2 = 0.5$). [22] The ED and ES LV volume/regurgitant volume relationships in our study (Figure 4) are also surprisingly linear. First, the linear nature of these relationships effectively proves the hypothesis that regurgitant volume effects LV volume after postero-lateral MI. Further interpretation is difficult except to note that pure Starling compensation for the mitral regurgitation would have produced a slope of 1.0 for the LV volume at ED/regurgitant volume relationship and a slope of 0 for the LV volume at ES/regurgitant volume relationship. The fact that slopes are 1.37 and .5 is probably related to the remodeling process.

LV remodeling associated with CIMR

LV volume index at end-diastole and end-systole increased rapidly until 8 weeks and then increased more slowly until 16 weeks. These results are consistent with those of Liel-Cohen et al [7] and Guy et al. [3] However, those studies followed sheep for 8 weeks after MI and would not have seen the decreased rate of remodeling between 8 and 16 weeks. It should also be noted that LV volume index is affected by animal growth and the decreased rate of remodeling that we observed between 8 and 16 weeks may in part be due to animal growth (increase in weight) that occurred in the late post-MI period.

There is increasing evidence that it is stress in the cross fiber direction that causes eccentric or volume overload type hypertrophy. [23, 24] However, it is unclear to what extent MR contributes to fiber and cross fiber stress in the borderzone and remote myocardium of the LV with CIMR. Streicher calculated wall stress using a force balance equation described by Janz [25] and found diastolic stress in the circumferential direction to be 2 times higher in sheep 8 weeks after MI with CIMR (782 mm Hg) than in sheep with MI involving circumflex marginal branches 1 and 2 that did not develop MR (387 mm Hg). [26] Although

finite element-based calculations of fiber and cross-fiber stresses are preferred [27], Streicher's results and the results presented here suggest that MR contributes significantly to the diastolic stress elevation in the borderzone and remote myocardium in CIMR.

Myocardial infarction is also associated with progressive remodeling of the infarct borderzone. This has been clearly demonstrated by Jackson and colleagues in anterior LV wall after antero-apical MI [28] but probably occurs in the lateral wall after postero-lateral MI also. For instance, Rodriquez et al. measured the borderzone strain associated with postero-lateral ischemia in sheep and found an increase in circumferential-radial shear and fiber-sheet strains. [29] Abnormal strain patterns presumably also occur after postero-lateral MI and may be the trigger for progressive borderzone remodeling and reduced borderzone contractility.

Implications for mitral valve repair

There is no consensus in animal and clinical studies about the ability of mitral valve repair to reverse the LV remodeling that occurs with CIMR. Matsuzaki et al recently found that mitral annuloplasty does not affect remodeling when performed 8 weeks after postero-lateral MI in sheep. [17] On the other hand, Beerli et al did demonstrate return to baseline LV volume when left atrial to LV shunt (MR equivalent) was occluded 6 weeks after MI. [5, 6] The reason for the difference is unclear but suggest that the amount of ischemic MR needs to be greater than mild in order to achieve an effect (remodeling) that can be reversed by mitral repair.

Repair of moderate CIMR at the time of coronary bypass in patients is also controversial. LV size and ejection fraction are significantly improved in patients with CIMR that are treated with coronary bypass (CABG) + mitral valve repair. [30] However, mortality in patients treated with CABG + mitral valve repair is not improved. [31, 32] As a consequence, an NIH sponsored clinical trial of CABG or CABG + mitral repair in patients with moderate CIMR is underway. [33]

Conclusion

We found that mitral regurgitation accelerates LV remodeling after postero-lateral MI. Further studies are needed to determine whether mitral valve repair is able to slow or reverse MI remodeling after postero-lateral MI.

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Figure 1.

A representative long-axis MRI image of the LV 8 weeks after MI. Endo (endocardial contour) and Epi (epicardial contour) contours have been manually traced and LV long and short axis diameters were measured.

Figure 2.
The change in RegurgVolume Index (A) and RegurgFraction (B) over time. The dashed line in panel A is the division between mild and moderate MR. [20]

Figure 3. Relationship between RegurgVolume Index and LV volume Index at end-diastole (A) and end-systole (B) for all data points. Black solid lines are linear regression.

Figure 4. Relationships between time after MI and LV volume Index at end-diastole (A) and LV volume Index at end-systole (B). *: $p < 0.05$ by linear mixed-effects model regression (Equation 6).

Figure 5. Relationships between time after MI and LV sphericity (A) and LV wall mass (B). *: $p < 0.05$ by linear mixed-effects model regression (Equation 6).

Table 1

Sheep weight, LV pressure, LV volume and amount of MR 2 weeks before and 2, 8 and 16 weeks after postero-lateral MI.

Time (week relative to MI)	0	2	8	16
Animal weight [Kg]	53.2±4.4	53.9±2.7	59.4±2.4 ^{*†}	67.0±4.5 ^{*‡}
LV Pressure at ES [mm Hg]	90.8±3.0	88.4±10.8	93.4±4.1	88.0±5.6
LV Pressure at ED [mm Hg]	5.7±1.3	6.9±1.5	6.5±1.4	6.6±2.6
Regurgitant Volume [ml]	4.2±5.3	8.3±9.0	15.6±13.0 [*]	19.0±10.8 ^{*†}
Regurgitant Fraction [%]	1.5±4.0	15.0±16.1	24.8±19.2 [*]	28.9±13.8 ^{*†}
Short axis [mm]	44.0±4.1	48.5±3.7	51.5±4.5 [*]	50.3±4.5 [*]
Long axis [mm]	87.2±4.1	88.9±2.5	90.1±3.4	90.9±3.4
Wall thickness [mm]	10.1±0.8	9.9±1.2	9.5±1.1	10.1±1.2
LV Volume at ED [ml]	83.9±17.1	109.8±15.7 [*]	122.5±22.4 [*]	132.3±22.7 ^{*†}
LV Volume at ES [ml]	40.4±10.3	61.2±15.5 [*]	63.6±16.1 [*]	69.4±2.6 [*]
LV Wall Volume [ml]	140.6±16.6	158.9±27.6	155.3±9.8	167.2±19.4 [*]
Sphericity [%]	50.5±4.1	54.7±4.3	57.2±5.3 [*]	55.4±4.8 [*]

^{*}=p<0.05 vs Week 0,

[†]=p<0.05 vs Week 2 and

[‡]=p<0.05 vs Week 8.

Table 2

Results (standardized coefficients and p values) of the linear mixed-effects model regression (Equation 6).

	RegurgVolume index		%Infarct	
	Standardized Coefficient	p value	Standardized Coefficient	p value
Short axis index [mm/m ²]*	0.067	p<0.0001	0.049	p=0.0026
Long axis index [mm/m ²]		p=NS	-2.001	p=0.0066
Wall thickness index [mm/m ²]		p=NS		p=NS
LV Volume @ED index [ml/m ²]*	0.151	p<0.0001	0.069	p=0.0156
LV Volume @ES index [ml/m ²]*	0.123	p=0.0086	0.122	p=0.0307
LV wall volume index [ml/m ²]		p=NS		p=NS
Sphericity [%]*	0.040	p=0.0007	0.060	p<0.0001

NS = not significant. Cross terms are not shown.

* denotes dependent variables where a natural log transformation was used.