Late Repair of Ischemic Mitral Regurgitation Does Not Prevent Left Ventricular Remodeling

Importance of Timing for Beneficial Repair

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Background—Ischemic mitral regurgitation (MR) is a frequent complication of myocardial infarction associated with left ventricular (LV) dilatation and dysfunction, which doubles mortality. At the molecular level, moderate ischemic MR is characterized by a biphasic response, with initial compensatory rise in prohypertrophic and antiapoptotic signals, followed by their exhaustion. We have shown that early MR repair 30 days after myocardial infarction is associated with LV reverse remodeling. It is not known whether MR repair performed after the exhaustion of compensatory mechanisms is also beneficial. We hypothesized that late repair will not result in LV reverse remodeling.

Methods and Results—Twelve sheep underwent distal left anterior descending coronary artery ligation to create apical myocardial infarction and implantation of an LV-to-left atrium shunt to create standardized moderate volume overload. At 90 days, animals were randomized to shunt closure (late repair) versus sham (no repair). LV remodeling was assessed by 3-dimensional echocardiography, dP/dt, preload-recruitable stroke work, and myocardial biopsies. At 90 days, animals had moderate volume overload, LV dilatation, and reduced ejection fraction (all \( P < 0.01 \) versus baseline, \( P = \text{NS} \) between groups). Shunt closure at 90 days corrected the volume overload (regurgitant fraction 6±5% versus 27±16% for late repair versus sham, \( P < 0.01 \) but was not associated with changes in LV volumes (end-diastolic volume 106±15 versus 110±22 mL; end-systolic volume 35±6 versus 36±6 mL) or increases in preload-recruitable stroke work (41±7 versus 39±13 mL mm Hg) or dP/dt (803±210 versus 732±194 mm Hg/s) at 135 days (all \( P = \text{NS} \)). Activated Akt, central in the hypertrophic process, and signal transducer and activator of transcription 3 (STAT3), a critical node in the hypertrophic stimulus by cytokines, were equally depressed in both groups.

Conclusions—Late correction of moderate volume overload after myocardial infarction did not improve LV volume or contractility. Upregulation of prohypertrophic intracellular pathways was not observed. This contrasts with previously reported study in which early repair (30 days) reversed LV remodeling. This suggests a window of opportunity to repair ischemic MR after which no beneficial effect on LV is observed, despite successful repair. (Circulation. 2013;128[suppl 1]:S248-S252.)

Key Words: heart disease, ischemic ■ mitral valve regurgitation ■ remodeling

ls ischemic mitral regurgitation (MR) is caused by altered left ventricular (LV) geometry and function and doubles heart failure and mortality after myocardial infarction (MI). Still common despite improvement in revascularization and medical treatment after MI, its treatment remains frustrating and controversial. Expansion of infarcted tissue begins acutely after MI, but a more gradual remodeling also involves noninfarcted areas. Initially compensatory, this process can become maladaptive as the ventricle enlarges and contracts poorly, with reduced survival. Although severe nonischemic MR has been shown to promote LV remodeling and increase mortality, even mild or moderate ischemic MR has been associated with poorer prognosis. We have previously demonstrated that moderate MR, simulated by an LV-to-left atrial (LA) shunt, added to a small anteroapical MI (causing no intrinsic MR) causes greater ventricular remodeling than a comparable infarction alone, with an earlier transition to a failure phenotype. Whole-heart changes parallel cellular and molecular abnormalities in the noninfarcted myocardium, reflecting the complex remodeling process. These molecular events progress differently after MI and moderate volume overload than...
with comparable infarction alone, with an initial rise in pro-
 hypertrophic and antiapoptotic signals (specifically, the Akt-
 phosphatidylinositol 3'-kinase and gp130-janus kinase (JAK)/
 signal transducer and activator of transcription 3 (STAT3)
 pathways), followed by their exhaustion. In the same model,
 early repair (after 1 month) of the MR-equivalent LV-to-LA
 shunt prevents downregulation of these compensatory path-
 ways and induces LV reverse remodeling manifested by nor-
 malization of both functional and anatomic parameters, also
 consistent with other ischemic MR models and therapeutic
 approaches. However, it is not known whether the molec-
 ular alterations and LV remodeling can be reversed by a late
 intervention done when the prohypertrophic and antiapoptotic
 signals are already downregulated.

Based on this observed biphasic molecular response in isch-
 emic MR, we specifically hypothesized that late MR repair
 would not result in LV reverse remodeling. This was tested
 using our previously described animal model of ischemic MR
 combining an apical MI and an LV-to-LA shunt, with shunt
 ligation at 3 months after MI to simulate MR repair.

Methods

Ischemic MR Model

A previously described ischemic MR model was created in 12 adult
 Dorsett hybrid sheep (weight >45 kg). This model, combining an
 apical infarction by distal left anterior descending coronary artery
 ligation (not causing MR by itself) and an LV to LA shunt (8-cm
 long, 8-mm diameter–reinforced Teflon graft with a cross-sectional
 area of 50 mm² implanted into the LV base and left atrial appendage
) (no repair group). The animals were observed for an average of 6
 more weeks and euthanized on day 135 (Figure 1). Has been shown to produce standardized and
 consistent MI size and moderate volume overload. Ninety days after
 the initial surgery, a second thoracotomy was repeated, and sheep
 were randomized to shunt closure (late repair group) or sham surgery
 (no repair group). The animals were observed for an average of 6
 weeks more and euthanized on day 135 (Figure 2). The 90 days late
 repair timing was chosen on the basis of previous studies in the same
 model showing exhaustion of prohypertrophic compensatory path-
 ways at this time. Animal studies conformed to National Institutes
 of Health guidelines (National Research Council, Washington, DC,
 1996) and were approved by the Institutional Review Board.

Echocardiography Analysis

Standard 2-dimensional and full-volume 3-dimensional data sets
 were obtained epicardially at each time point (baseline, 90 days, and
 135 days) using high-frequency (S5, X3) probes and a Philips iE33
 scanner (Andover, MA). Shunt patency or closure was confirmed by
color flow Doppler. Three-dimensional analysis was performed
 blinded to group and time point using the custom software Omni4D
 (MD Handschumacher) as previously described. LV end-diastolic
 and end-systolic volumes (ESV) were measured and LV ejection frac-
tion computed. Regurgitant volume was calculated as total 3-dimen-
sional stroke volume (end-diastolic volume–ESV) minus forward
 aortic stroke volume calculated by pulse wave Doppler and the con-
tinuity equation. Regurgitant volume and fraction, therefore, included
 the regurgitant flow through the LV-to-LA shunt, but also accounted
 for any additional functional MR that could have occurred secondary
to LV dilatation in the context of combined MI and volume overload.

LV Pressure–Volume Analysis

At baseline and day 135, a high-fidelity conductance catheter
 (Scisense, Ontario, Canada) was inserted transapically to record LV
 maximal dP/dt and pressure–volume relationship under different
 preload conditions by simultaneously partially occluding the inferior
 vena cava, with subsequent computation of preload-recruitable stroke
 work (PLR SW), a preload independent measure of LV systolic
 contraction.

Tissue Samples and Molecular Analysis

Myocardial needle biopsy was performed at baseline before model
 creation, and both peri-infarct and remote myocardium were biopsied
 at days 90 and 135. We measured levels of pAKT (protein kinase B),
central in the hypertrophic process, and pSTAT3, a critical node in
 the hypertrophic stimulus by cytokines. Both these, at their respective
 levels (cytosol and membrane), are important crosstools in prohy-
 pertrophic signaling. Western blot analysis was performed on cell
 lysates from biopsies at baseline, day 90, and day 135. pSTAT3 and
 anti-phosphoAkt (Santa Cruz Biotechnology, Santa Cruz, CA) were
detected with peroxidase-conjugated anti-mouse IgG and chemilumi-
nescence, with α-actin as the housekeeping control. Integrated blot
 pixel density was assessed using standard software (ImageJ; National
 Institutes of Health, Bethesda, MD).

Statistics

Continuous variables are expressed as mean±SD. Differences within
 and between groups at different time points were assessed with
 repeated-measures ANOVA. Rank-based ANOVA was performed
 when normality was excluded by the Shapiro–Wilk test. P<0.05 was
 considered significant. Based on previous data with the same model,
it was calculated that a sample size of 6 per group would provide
 ≥80% power (α level, 0.05) to detect an effect comparable with early
 MR repair between groups (25 mL·mm Hg in preload-recruitable
 stroke work and 40 mL in ESV). Statistical analysis was performed
 with Stata/IC 11.2 (StataCorp LP, TX). The authors had full access to
 and take full responsibility for the integrity of data.

Results

LV Volumes and Function

A total of 16 sheep underwent the initial procedure of MI+MR. Four
 sheep died suddenly within the first 48 hours, presumably from
 malignant arrhythmia. A total of 12 sheep completed the
 protocol successfully, without death occurring after random-
 ization of MR repair versus sham procedure. As expected, the

Figure 1. Schematic representation (left) and perioperative view
(right) of the left ventricle-to-left atrial appendage shunt. MR
indicates mitral regurgitation; and MI, myocardial infarction.

Figure 2. Protocol summary with model creation at day 0, randomization to late repair or sham procedure at day 90,
and euthanasia at day 135. It has been previously shown that an early repair at 30 days is beneficial to stop and reverse
the left ventricular remodeling cascade. MR indicates mitral regurgitation; and MI, myocardial infarction.
initial procedure of MI+MR resulted in a progressive increase in LV end-diastolic volume and ESV (both $P<0.01$ versus baseline), a decrease in LV ejection fraction ($P<0.01$ versus baseline), and a moderate volume overload (regurgitant volume $15\pm4$ mL; regurgitation fraction $34\pm8\%$) at 90 days, with no significant difference between groups (Figure 3). Shunt ligation at 90 days in the late repair group successfully corrected the volume overload, whereas the no repair group had persistent regurgitation until euthanasia (regurgitant volume $2a\pm2$ versus $12\pm7$ mL for late repair versus no repair, $P=0.007$). However, this late correction did not prevent progression of LV remodeling at 135 days, and both end-diastolic volume ($106\pm15$ versus $110\pm22$ mL for late repair versus no repair, $P=0.72$) and ESV ($69\pm15$ mL versus $70\pm16$ mL for late repair versus no repair, $P=0.95$) were further increased at euthanasia with reduced LV ejection fraction ($35\pm6$ versus $36\pm6\%$ for late repair versus no repair, $P=0.70$), with no significant difference between groups (Figure 3). LV hemodynamics showed the same pattern: preload-recruitable stroke work was significantly and equally reduced at euthanasia in both groups (Figure 4; $41\pm7$ versus $39\pm13$ mL·mm Hg, $P=0.70$). Maximal $dP/dt$ also declined over time comparably in both groups at euthanasia ($803\pm210$ versus $732\pm194$ mm Hg/s, $P=0.56$).

**Molecular Analysis**

Western blot–integrated density of prohypertrophic markers pAKT and pSTAT3 at 3 time points is displayed in Figure 5. As expected, both groups had similarly decreased signals for these markers at 90 days. However, late repair did not result in recovery, and both groups were equally depressed at day 135 ($P=0.16$).

**Discussion**

In this study, we show that late correction of a moderate volume overload 3 months post-MI does not reverse or prevent further LV remodeling and dysfunction, with consistent outcomes at the functional and molecular levels. These results contrast with a previously published study, in which early (1 month) repair was associated with complete normalization of ventricular volume, hemodynamic alteration, and molecular alteration.

Despite its clear association with poorer prognosis, treatment of ischemic MR remains highly controversial. Both clinical and experimental studies yield conflicting results. Part of this controversy is attributable to the complex nature of LV remodeling associated with ischemic MR: the MI initially causes the MR, but both MI and MR can contribute to cellular and functional changes in the noninfarcted LV. The relative contribution of MI and MR has been difficult, if not impossible, to separate in clinical studies. Other confounders relate to MR surgical correction, often performed with simultaneous coronary revascularization and with the frustrating problem of recurrent MR, treating the volume overload often only partially or temporarily. This animal model of apical MI with LV-to-LA shunt can help resolve these difficulties. By isolating the effect of moderate volume overload on comparable MI size and location, it previously demonstrated the additional contribution of moderate MR to LV remodeling. The second advantage is the adequate and persistent correction of volume overload by shunt ligation, simulating a successful and minimally invasive MR repair. In this controlled environment, the current experimental study provides another possible explanation for discrepancies between clinical studies by suggesting that a successful surgical correction can produce variable results if not performed in a timely manner.

This variable response to correction at different time points needs to be related to the previously observed biphasic molecular response in the myocardium after MI and MR. Cardiac remodeling in ischemic MR is dynamic: increased apoptotic tone (caspase-3) has been shown in remote myocardium, partially counterbalanced by transiently increased...
prohypertrophic and antiapoptotic pathways: the gp130-STAT3 pathway is related to cytokine-mediated hypertrophy, and protein kinase B (Akt) is a serine/threonine-specific protein kinase promoting growth factor–mediated cell survival and hypertrophy. Signaling of both pathways is increased after MI, but the presence of moderate volume overload is associated with subsequent downregulation paralleling the transition to heart failure. Early MR repair when performed while gp130 and Akt are still overexpressed can interrupt the vicious remodeling cycle and reverse heart failure. The lack of success of the same procedure after downregulation of these compensatory pathways indicates a point of no return for LV remodeling in ischemic MR and suggests a limited time window to correct the MR, with less or no beneficial effect if the intervention is not performed within this interval. The persistent negative remodeling observed after late MR repair suggests that these profound molecular alterations not only prevent reversal of heart failure but could also contribute to further LV remodeling even after the correction of the initial volume overload.

Clinical Correlation and Future Studies
Clinical criteria to correct MR surgically are generally based on MR severity, LV dimensions, and function. Although clinically important and useful, these parameters might not be sufficient to capture the whole spectrum of LV remodeling or completely predict outcome after surgery for ischemic MR. Although the current study suggests that earlier repair is better to prevent LV remodeling, determining the best timing for intervention in a clinical setting will remain a challenge because each patient presents variable MI size, MR severity, and myocardial substrate and, therefore, an individual time window. Although preoperative echocardiography assessment can help predict procedural success in terms of MR correction and that parameters, such as LV dimension, can be useful to assess the remodeling, it is unclear at this point how well imaging (other than LV dimensions and function) and biomarkers can improve the prediction of ventricular response after successful MR repair. Another question will be whether and how current and future medical therapies can prolong the time during which beneficial repair can be performed. Well-designed clinical and experimental studies are needed to answer these relevant questions properly.

Limitations
While helping to understand the effects and potential implications of volume overload correction on LV remodeling, direct extrapolation to patients with ischemic MR cannot be made at this point. This animal model was designed to separate the results of MI and volume overload on LV remodeling and to study the effects of successful MR repair, but does not fully represent the clinical scenario. However, these results highlight the dynamic nature of LV remodeling in ischemic MR and the importance of timing when considering surgical intervention. Our power was sufficient to rule out changes of the magnitude observed by early repair, but the relative small sample size could not rule out a smaller beneficial effect of late repair compared with no treatment. Although we previously used this model to show the beneficial effects of early repair, LV volume was measured differently in the current study (real-time 3-dimensional echocardiography versus

Figure 4. Left ventricular dP/dt (A) and preload-recruitable stroke work (PLRSW) (B) at baseline and euthanasia, showing a similar pattern compared with the echocardiographic analysis: late volume overload correction at 90 days did not prevent loss of left ventricular function at 135 days.

Figure 5. Integrated density from Western blot normalized for α-actin. Top, pAKT levels showing comparable suppression in both groups at 90 and 135 days, without improvement in the late mitral regurgitation repair group. Bottom, Similar pattern is observed for pSTAT3. Downregulation of both molecules was, however, prevented by early repair at 30 days in a previous study.
Conclusions

In this ischemic MR animal model, late MR repair was not beneficial to prevent additional LV remodeling, in contrast to earlier repair. This suggests a point of no return after which no or limited beneficial effect of MR repair can be achieved, despite adequate correction of volume overload. The timing of valve repair in ischemic MR needs to be assessed in future clinical studies because this could, in part, resolve controversies and discrepant findings in this area.

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Disclosures

None.

References

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