Early Repair of Moderate Ischemic Mitral Regurgitation Reverses Left Ventricular Remodeling
A Functional and Molecular Study

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Background—Mitral regurgitation (MR) doubles postmyocardial infarction (MI) mortality. We have shown that moderate MR augments remodeling in an apical MI model (no intrinsic MR) with independent left ventricle-to-left atrial MR-type flow. We hypothesized that repairing moderate MR 1 month after MI reverses this remodeling.

Methods and Results—Anteroapical MIs were created in 18 sheep, and a left ventricle-to-left atrial shunt implanted in 12 (regurgitant fraction, 30%). Six sheep had the shunt closed at 1 month (repair group). Sheep were compared at baseline, and at 1 and 3 months. Sheep in the MI+MR (unrepaired) and repaired groups remodeled during the first month (120% increased left ventricular end-systolic volume [ESV; P<0.01]), but shunt closure reversed remodeling at 3 months, with end-diastolic volume (EDV) and ESV 135% and 128% of baseline versus 220% and 280% without repair (P<0.001). At 3 months, dP/dt and preload-recruitable stroke work were relatively maintained in the repaired and MI-only groups versus nearly 50% decreases without repair. Prohypertrophic gp130 and antiapoptotic pAkt increased followed by exhaustion below baseline without repair, but remained elevated at 3 months with repair or MI only. With repair, matrix metalloproteinase-2 decreased to 50% that without repair in remote and border zones at 3 months, and the matrix metalloproteinase inhibitor TIMP-4 increased dramatically.

Conclusions—Early repair of moderate MR in the setting of apical MI substantially reverses the otherwise progressive remodeling process, with reduced left ventricular volumes, relatively maintained contractility, persistently activated intracellular signals promoting hypertrophy and opposing apoptosis, and reduced matrix proteolytic activity. These findings are of interest for the current controversy regarding potential benefits of repair of MR after MI. (Circulation. 2007;116[suppl I]:I-288–I-293.)

Key Words: mitral valve ■ myocardial infarction ■ regurgitation ■ remodeling ■ surgery

Expansion of infarcted tissue begins acutely after myocardial infarction (MI), but a more gradual remodeling process also involves noninfarcted areas; initially compensatory, this process becomes maladaptive, as the ventricle enlarges and contracts poorly with reduced survival. MI also causes ischemic mitral regurgitation (MR) by altering ventricular geometry and function, doubling the risk of death. Severe nonischemic MR has been shown to promote left ventricular (LV) remodeling and reduce survival. We have previously demonstrated (unpublished data) that moderate MR, simulated by a left ventricle-to-left atrial 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 that reflect the complex remodeling process. These molecular events also progress differently with MR than with comparable infarction alone, with an initial rise in prohypertrophic and antiapoptotic signals followed by their exhaustion. Most experimental models of post-MI remodeling use inferoposterior MIs, but this necessarily links the MI-induced remodeling to the development of MR. The shunt model allows MR to be varied independently in the presence of MI and without interventions such as infarct patching that might themselves influence remodeling.
There is active controversy whether ischemic MR causes excess left ventricular (LV) remodeling, and whether repairing it reverses this process.18–20 Our hypothesis was that, in view of the excess remodeling induced by moderate ischemic MR, repairing it at an early phase may reverse the remodeling process. The shunt model is ideally suited to answer this question, because it allows repair of MR simply by ligating the shunt without requiring cardiopulmonary bypass.

**Methods**

**Mitrral Regurgitation Model**

A modification of the experimental MR model of Braunwald21 and Rankin22 was implemented using an 8-cm long, 8-mm diameter reinforced polytetrafluoroethylene graft (Edwards, cross-sectional area 0.50 cm²) implanted under sterile conditions into the midlateral LV and LA appendage with intramural physician stiffened with epoxy resin (Figure 1). The regurgitant flow was confirmed during each thoracotomy (see subsequently) using a Transonic flow probe and color Doppler. The standardized shunt diameter and length consistently produced moderate MR (regurgitant fractions of approximately 30%).23 Animals were treated with heparin (3 days) and then oral aspirin.

**Animal Studies**

A total of 18 male Dorsett hybrid sheep (20 to 30 kg) were loaded for 3 days with amiodarone (200 mg orally twice a day), anesthetized with thiopentothal (0.5 mL/kg), intubated, and ventilated at 15 mL/kg with 2% isoflurane–oxygen, receiving glycopyrrolate (0.4 mg intravenously) and prophylactic vancomycin (0.5 g intravenously) and amiodarone (150 mg intravenous drip). Surface electrocardiogram was monitored and a sterile left thoracotomy performed with pericardial cradle creation. A high-fidelity micromanometer-tipped catheter (Millar, Houston, Texas) was placed into the LV though the apical lateral myocardium. After baseline 2-dimensional and 3-dimensional echo imaging, an experimental LV-to-left atrial shunt was ligated at 30 days (the MR repair group); in the other 6 (the MI group) the shunt remained open for 90 days. Animal studies conformed to National Institutes of Health guidelines (National Research Council, Washington, DC, 1996) and were Institutional Review Board-approved.

**Results**

**Left Ventricular Volumes**

Although the MI+MR and MR repair groups had similar end-diastolic volumes at 1 month, end-diastolic volume was...
significantly reduced in the repaired group at 3 months (142.4±48 mL in the MR/MI group versus 57.1±9.2 mL in the MR repair group, *P*=0.01, Figure 2). End-systolic volumes were similarly reduced in the repaired relative to the unrepaired group (69.6±13.9 mL versus 29.9±1.8 mL, $P=0.02$, Figure 2B). End-diastolic and end-systolic volumes did rise at 1 month in the MR repair group, only to fall toward baseline at 3 months follow-up ($P<0.01$). LV ESV was also smaller at 3 months in the repaired group than in those with MI only never exposed to MR.

**Left Ventricular Function**

Peak positive dP/dt, a measure of global contractility, was similar in the 3 groups at 1-month follow-up (Figure 3). It decreased significantly in the MR/MI group at 3 months, whereas it was relatively maintained in the MR repair group similar to the MI-only group (685±38 mmHg/sec for MI+MR versus 1039±166 and 1081±250 mmHg/sec for MR repair and MI-only, $P=0.006$).

Preload-recruitable stroke work, a holosystolic contractility measure, was similarly depressed in the MI+MR repair group relative to the MR repair and MI-only groups (29.6±7.6 versus 56.2±15.3 and 64.2±19.6 mL·mmHg, $P=0.03$). This load-independent measure of LV contractility was chosen to address the concern that MR may mask LV dysfunction.

**Intracellular Signaling Pathways**

Gp130, a receptor upregulated in cardiac hypertrophy, decreased significantly in the MI+MR group at 3 months while remaining elevated in the MR repair group (Figure 4A). Akt (protein kinase B), a key enzyme promoting hypertrophy and opposing apoptosis, also fell below baseline at 3 months in the MI+MR group versus significant elevation in the MR repair group at that time (Figure 4B). In contrast, caspase-3, the final common enzyme for caspase-dependent proapoptotic pathways, remained elevated at 3 months in the MI+MR group but returned to baseline in the MR repair group (Figure 4C).

**Extracellular Matrix Enzymes**

In the repair group at 3 months, MMP-2, a gelatinase upregulated in heart failure, significantly decreased below baseline and below levels in the MI+MR and MI-only groups in both remote and border zones (Figure 5).

Tissue inhibitor of MMPs (TIMP)-4, downregulated in heart failure, was prominently upregulated in the MR repair group at 3 months.

**Discussion**

Post-MI remodeling aims to preserve cardiac output, including increased LV end-diastolic volume to augment preload. Cells in noninfarcted areas hypertrophy by adding contractile elements in series without increased wall thickness. This allows the LV to dilate, also promoted by sarcomere slippage, MMP activation with extracellular matrix degradation, and acceleration of apoptotic cell death, culminating in systolic enlargement, extensive fibrosis, and LV failure, which predicts cardiac events. Volume overload increases wall stress, which can aggravate remodeling and upregulate MMPs, believed pivotal in altering the extracellular matrix in ways that promote dilatation. Conversely, LV unloading reverses the functional and cellular stigmata of cardiac failure and remodeling.

Mitral regurgitation, caused by alterations in ventricular geometry and function after MI, can itself initiate the remodeling cascade and causes progressive deterioration of ventricular function at a cellular and molecular level. We have previously demonstrated (unpublished results) that adding even only...
moderate MR to a small anteroseptal MI aggravates the morphological, functional, cellular, and extracellular stigmata of remodeling. Because MR is both a cause and result of LV remodeling, it can potentially exacerbate the vicious cycle spiraling down to cardiac failure unless remodeling or MR is reversed.7,35–38

Regarding clinical implications, knowing whether the parallel occurrence of MR and MI causes more pronounced remodeling is critical, because at least MR can be eliminated by repairing or replacing the valve, thus relieving the volume overload induced by it. Separating these 2 dynamic processes in an experimental model is a challenge because in most existing models, they are linked. One recent study of inferior MIs, in fact, concluded that prevention of ischemic MR does not influence the outcome of remodeling19 despite benefits in nonischemic models13 and concerns in nonischemic patients.39 In our model, we therefore implanted an LV-to-left atrial shunt, which created a moderate and standardized MR-like regurgitant flow, independent of a modest anteroseptal MI that by itself does not cause MR. This allowed us to simulate mitral valve repair readily at 1 month by ligating the shunt, thus avoiding the complicating factor of cardiopulmonary bypass needed for actual valve repair.

We sought to determine whether repairing moderate MR at an early stage reverses LV remodeling. This hypothesis is at the center of intense controversy. Clinical work has produced mixed results, mainly in patients with LV dysfunction. Prifti and colleagues retrospectively assessed 99 patients with grade II–III ischemic MR; those who underwent mitral repair had improved survival at 3 years compared with controls.40 Wu and colleagues, on the other hand, did not find survival benefit from repairing MR in patients with LV dysfunction,41 although the frequency of persistent or recurrent MR postrepair may account for the apparent lack of benefit.37,38,42 The model in this study is ideal to address this quandary, because it allows mitral repair that is both durable and independent of other procedures which may alter outcome, such as coronary revascularization.

In contrast to progressive changes in the LV, several mediators of the hypertrophic process undergo biphasic changes in the noninfarcted myocardium of animals with MI+MR (Figures 4A–B). These include gp130, a glycoprotein that forms heterodimers to produce different receptors of the IL-6/CT-1/LIF family, activation of which has been linked to cardiomyocyte hypertrophy43 and reduction of which has been associated with transition from hypertrophy...
to failure. Akt, or protein kinase B, is a serine–threonine kinase activated by several prosurvival and prohypertrophic factors, including cardiotophin-1, acting through the gp130-containing receptor or growth factor receptors activating phosphoinositide-3 kinase. Constitutive Akt activation in an ischemia–reperfusion model reduced cell death and improved function. Like gp130, reduced Akt levels are related to increased apoptosis and transition from compensatory hyper- trophy to a failure phenotype. In our model, we have demonstrated that although after 1 month these species were upregulated in all 3 groups, consistent with a prohypertrophic tone at that time, they declined significantly in animals with persistent MR but not in those with MR repair. On the other hand, caspase-3, the final common node for all caspase-dependent apoptosis, was upregulated at 3 months in the MI + MR group but declined to baseline in the MR repair group. Taken as a whole, the intracellular results signify a higher prohypertrophic and antiapoptotic intracellular milieu in the MR repair group. The initial compensatory response, followed by progression to failure, is consistent with work previously published by Meersohn.

MMP-2 is a gelatinase that degrades extracellular matrix and especially basement-membrane components and is upregulated in heart failure. MMP-2 was significantly downregulated below baseline in the MR repair animals at 3 months while having maintained levels in the MI + MR animals. This could signify active suppression of the extracellular matrix proteolytic activity of this enzyme after MR repair, consistent with reverse remodeling. At the same 3-month time point, TIMP-4, a cardiac-specific MMP inhibitor, rose dramatically in the MR repair group compared with the other groups. This would indicate active suppression of matrix proteolytic activity after MR repair, consistent with reverse remodeling and matrix stabilization.

An unexpected observation is that the degree of LV remodeling at 3 months in the group with MI and repaired MR was less than in the group with MI only unexposed to MR, with a significantly lower LV end-systolic volume (Figure 2B). This raises the possibility that MR activates processes that lead to remodeling as well as compensatory opposing mechanisms. Removing the MR and reducing wall stress might then leave a persisting momentum of reverse remodeling that maintains a smaller LV. This is consistent with the continuing rise in gp130, Akt, and TIMP-4 in the MR repair group from 1 to 3 months (Figures 4A–B and 5B), the decline of caspase-3 to baseline (Figure 4C), and the decline in MMP-2 (Figure 5A).

This study has several limitations. Ischemic MR affecting a native valve often progressively increases but is inherently linked to the underlying MI and not standardized. Based on the study motivation, it was critical to separate the 2 processes of infarction and regurgitation to determine the incremental role of MR and its repair most directly, and to do so with a standardized orifice, which provided stable regurgitant fractions of approximately 30% throughout the study. Because we sought only a proof of concept, we did not assess different time points of MR repair. Specifically, we did not seek to determine whether there is a “point of no return” after which repairing the valve would not cause reverse remodeling any longer. This is the subject of upcoming studies. One needs to be cautious about directly extrapolating the relevance of these results to the “real-life” clinical setting. This needs to be addressed in a controlled, randomized clinical study, for which these results, however, present an important rationale.

In summary, this study demonstrates that repairing MR accompanying MI after 1 month reverses ventricular remodeling at 3 months compared with persistent MR. This is the case even for MR that is only moderate, most typical of the ischemic situation, for which the greatest uncertainty exists regarding impact on the heart and need for intervention. The changes at the level of the whole heart parallel cellular and molecular abnormalities in the noninfarcted myocardium that reflect the complex remodeling process. Adverse molecular events that typify a remodeling myocardium are suppressed after MR repair to levels comparable to those seen in MI alone, whereas compensatory mechanisms, including matrix stabilization, remain activated. Therefore, this study suggests that repairing moderate MR early after MI reverses the remodeling process exacerbated by mitral regurgitation in this setting.

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Disclosures
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