Published in final edited form as:

JACC Cardiovasc Interv. 2015 February ; 8(2): 355–363. doi:10.1016/j.jcin.2014.09.016.

Efficacy of Polymer Injection for Ischemic Mitral Regurgitation:

Persistent Reduction of Mitral Regurgitation and Attenuation of Left Ventricular Remodeling

Xin Zeng, MD, PHD^{*}, Lin Zou, MD, PHD^{*}, Robert A. Levine, MD^{*}, J. Luis Guerrero, BS[†], Mark D. Handschumacher, BS^{*}, Suzanne M. Sullivan, BS[†], Gavin J.C. Braithwaite, PHD[‡], James R. Stone, MD, PHD[§], Jorge Solis, MD^{*}, Orhun K. Muratoglu, MD^{||}, Gus J. Vlahakes, MD[†], and Judy Hung, MD^{*}

^{*}Cardiac Ultrasound Laboratory, Massachusetts General Hospital, Boston, Massachusetts

[†]Cardiac Surgery Division, Massachusetts General Hospital, Boston, Massachusetts

[‡]Cambridge Polymer, Inc., Boston, Massachusetts

[§]Department of Pathology, Massachusetts General Hospital, Boston, Massachusetts

^{||}Biomaterials Laboratory, Department of Orthopedic Surgery, Massachusetts General Hospital, Boston, Massachusetts

Abstract

OBJECTIVES—The aim of this study was to examine the chronic effects of polyvinyl-alcohol (PVA) injection on mitral regurgitation (MR) reduction, mitral valve geometry, and left ventricular (LV) remodeling in a chronic ischemic MR sheep model.

BACKGROUND—Previous studies have demonstrated acute efficacy of PVA hydrogel polymer injection into infarcted myocardium underlying the papillary muscle to relieve MR by papillary muscle repositioning. However, the chronic efficacy of PVA injection in the chronic infarction setting remains unclear.

METHODS—Sixteen sheep developed chronic MR 8 weeks after induced inferoposterior myocardial infarction. Ten consecutive sheep underwent PVA injection (PVA group) and 6 sheep served as control subjects with saline injection. Epicardial 2-/3-dimensional echocardiography was performed at the baseline, chronic MR (pre-injection), and sacrifice (8 weeks after injection) stages.

RESULTS—Both groups were comparable at the baseline and chronic MR stages. At sacrifice, MR decreased from moderate to trace or mild (vena contracta: 0.17 ± 0.08 cm vs. 0.56 ± 0.10 cm, $p < 0.001$) in the PVA group but progressed to moderate to severe in the control group. End-systolic and -diastolic volumes remained stable in the PVA group but increased significantly in the control group (both $p < 0.05$). At sacrifice, compared with the control group, the PVA group had

REPRINT REQUESTS AND CORRESPONDENCE: Dr. Judy Hung, Massachusetts General Hospital, Cardiac Ultrasound Laboratory, Blake 256, 55 Fruit Street, Boston, Massachusetts 02114. jhung@mgh.harvard.edu.

All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

APPENDIX For accompanying videos, please see the online version of this paper.

significantly less left ventricular remodeling (end-systolic volume: 41.1 ± 10.4 ml vs. 55.9 ± 12.4 ml, $p < 0.05$), lower MR severity (vena contracta: 0.17 ± 0.08 cm vs. 0.60 ± 0.14 cm, $p < 0.01$), and favorable changes in mitral valve geometry.

CONCLUSIONS—Polymer injection in a chronic ischemic MR model results in persistent reduction of MR and attenuation of continued left ventricular remodeling over 8 weeks of follow-up.

Keywords

echocardiography; mitral regurgitation; myocardial infarction; remodeling

Ischemic mitral regurgitation (IMR) is a common complication of myocardial infarction (MI). Mild or greater IMR occurs in 42% to 50% of patients within 30 days following acute MI, among which about 12% of patients had moderate or greater MR (1,2). Importantly, the presence of even mild MR is associated with increased mortality risk and reduced survival (3). Additionally, up to 50% of patients with LV systolic dysfunction from either ischemic or nonischemic etiologies have moderate or greater MR, representing high-risk subsets (4). Currently, surgical management of moderate or severe IMR is recommended by the American College of Cardiology/American Heart Association guidelines (5). Ring annuloplasty is the most commonly used procedure, which downsizes the mitral annulus to improve coaptation and reduce the MR. However, larger series show there is an approximately 30% recurrence rate of IMR 1 year after mitral repair and the prevalence increases with time (6). Treatment options for IMR have recently been expanded with the development of percutaneous mitral valve repair.

The mechanisms of IMR relate to leaflet tethering due to papillary muscle (PM) displacement secondary to ischemic left ventricular (LV) wall distortion, with a contribution from annular dilation. Either surgical or percutaneous mitral valve repair does not address the ventricular problem, so that leaflet tethering and continued LV remodeling appear to account for the high incidence of recurrent MR (7,8). On the other hand, surgical strategies that directly target the LV distortion have demonstrated efficacy in reducing recurrent MR by attenuating leaflet tethering, such as infarct plication or external constraint using a patch with an adjustable balloon device over the infarcted LV (9). However, these techniques remain relatively invasive.

Injection of polymers into an infarcted myocardium is a novel approach to treat IMR, with the potential to not only reduce IMR but also to stabilize adverse LV remodeling by acting as a tissue-bulking agent. Polyvinyl alcohol (PVA) polymer is a biocompatible and biologically inert material that can be formulated to be injectable and form a stable solid gel once it has been injected into the myocardium. Our previous studies have demonstrated acute efficacy of PVA hydrogel polymer injection into an infarcted myocardium underlying the PM to relieve IMR in both acute and chronic IMR models (10,11). The mechanism of MR reduction immediately after PVA injection is associated with repositioning of the papillary muscle. In the present study, we aim to examine the long-term efficacy of PVA injection in MR reduction and LV remodeling in the setting of chronic MI. IMR is most often encountered in the chronic infarction setting and both MR recurrence and LV remodeling are

of particular relevance to adverse outcomes. We hypothesized that chronic localized PVA hydrogel injection can stabilize the mitral valve-LV spatial relationship, resulting in the beneficial effects on persistent MR reduction and attenuation of LV remodeling in the setting of chronic MI.

METHODS

STUDY DESIGN

The study design is illustrated in Figure 1. As detailed by Llaneras et al. (12), inferoposterior MI was created in Polypay sheep by ligation of the second and third circumflex marginal branches. A chronic IMR model was produced 8 weeks after ligation, and animals underwent a second thoracotomy for injection of PVA polymer (PVA group) or saline (control group). Animals were observed for a further 8 weeks after injection. A third thoracotomy was performed to evaluate the chronic efficacy of the treatment and then the animals were euthanized.

Epicardial 2-dimensional (2D) and 3-dimensional (3D) echocardiography were performed at baseline, at the chronic MR stage (before injection), and at sacrifice (8 weeks after injection). Hemodynamic assessment was performed at the chronic MR stage and at sacrifice. This study was approved by our institutional Animal Care Committee.

PVA HYDROGEL POLYMER INJECTION

Preparation and injection of PVA hydrogel was performed as previously described (10,11). An 11% PVA hydrogel aqueous solution (Cambridge Polymer Group, Inc., Boston, Massachusetts) was pre-formulated, sterilized, and stored in 10-ml syringes at room temperature (20°C to 30°C) as a solid gel. This PVA formulation was designed to gel at or near body temperature (below 45°C). The PVA hydrogel syringes were heated to over 90°C in a water bath to achieve liquid state and then allowed to cool to 39°C to 40°C before injection. Location of injection was identified to be within the scar tissue of the inferoposterior wall, as guided by direct visualization of the infarcted myocardium. Once identified, this area was manually compressed inward with a displacement of about 1 cm with real-time echocardiographic imaging to confirm reduction in MR. The PVA hydrogel was then injected into the target area underlying the PM using an 18-gauge short-bevel needle at a 45° angle relative to the myocardium (Figure 2). The amount of polymer injected can be guided by echocardiographic assessment of MR if satisfying reduction is achieved. Each injection contained 1 to 2 ml of PVA hydrogel. If MR remained greater than mild after a total of 2 ml of PVA injected, a repeat injection was performed in an adjacent region within 1 to 2 cm of the initial injection site. Maximal PVA volume injected did not exceed a total of 5 ml.

The control group was treated with an injection of saline into the target area with a similar volume as that of injected PVA.

ECHOCARDIOGRAPHY

Epicardial 2D and 3D echocardiography were performed using iE33 ultrasound system equipped with S5-1 and X3-1 transducers (Philips Medical Systems, Andover, Massachusetts). The 2D measurements included vena contracta (VC) width for MR quantification (10), LV end-systolic volume (ESV) and end-diastolic volume (EDV) by the biplane Simpson method, and left atrial (LA) volume by biplane area-length method. LV ejection fraction (EF) was calculated. The 3D quantification of MR severity by measuring the VC area was performed using Philips Qlab software as previously described (13).

The 3D mitral valve geometry was assessed at midsystole using customized software Omni4D (M.D. Handschumacher). Mitral annular area, leaflet closure area, tenting volume, tethering length, as well as interpapillary muscle distance (IPMD), defined as the distance between the medial and lateral PM tips, were traced and computed as described previously (11,14).

HEMODYNAMIC ASSESSMENT

Electrocardiogram was used to monitor arrhythmias and ischemic electrocardiographic changes. Acquisition and analysis of the hemodynamic data were performed using iWorx LabScribe2 software (iWorx, Inc., Dover, New Hampshire). A 7.0-F conductance catheter (Scisense Inc., Ontario, Canada) was inserted transapically to record LV end-systolic and end-diastolic pressure, maximal and minimum first derivative of pressure measured over time, and relaxation constant (by Weiss method). Temporary inferior vena cava occlusion was performed to evaluate changes in load-independent variables, including elastance (slope from the end-systolic pressure volume relationship), stiffness (slope from the end-diastolic pressure volume relationship), and slope from the preload-recrutable stroke work relationship.

HISTOLOGICAL STUDIES

The heart, brain, spleen, and kidney were excised for histological examination in a subset of 5 PVA-treated sheep after sacrifice to exclude embolization. Specimens were fixed in 10% formalin, and histopathologic examinations were performed on 5- μ m sections stained with hematoxylin-eosin.

SAMPLE SIZE AND POWER

We hypothesized that PVA injection would result in MR reduction from moderate to severe (VC width ≥ 0.5 cm) to trace or mild (VC width <0.3 cm), which is considered clinically significant. To demonstrate such change with 5% α error and 90% power, a minimum of 6 sheep per group was required.

STATISTICAL ANALYSIS

Measurements were reported as mean $\pm$ SD for continuous variables. Differences between groups were analyzed with unpaired Student *t* test. Differences in echocardiographic measurements among stages (baseline, chronic MR, and sacrifice) were analyzed by analysis of variance for repeated measures. Multiple pairwise comparisons were adjusted with

Bonferroni correction. Differences in hemodynamic measurements between stages were tested by paired *t* test. A 2-tailed probability value of 0.05 was considered significant. SPSS software was used for statistical analysis (SPSS Inc., Chicago, Illinois).

RESULTS

SAMPLE SIZES AND MORTALITY

Twenty-four sheep underwent ligation of left circumflex branches. Eight animals were excluded (3 sheep died acutely after MI due to malignant ventricular arrhythmia and 5 developed less than mild MR). A total of 16 sheep that developed moderate or greater MR 8 weeks after ligation were further studied. Ten consecutive sheep (41 ± 4 kg) were treated with an injection of PVA (3.4 ± 0.6 ml) and 6 sheep (42 ± 4 kg) were treated with an injection of saline (3.5 ± 0.5 ml). There was no sudden death after PVA or saline injection. All sheep were stable and survived up to over 8 weeks after injection before being sacrificed.

MR REDUCTION

Figure 3 shows the changes of MR severity in the PVA and control groups from the chronic MR stage to sacrifice. At the chronic MR stage, the MR severity was comparable in both groups. Acutely after PVA injection, MR decreased from moderate to trace or mild in all sheep; however, no beneficial effect was found in the control sheep after saline injection. Overall, there was persistent MR reduction 8 weeks after PVA injection (VC width: 0.17 ± 0.08 cm vs. 0.56 ± 0.10 cm, $p < 0.001$; VC area: 0.06 ± 0.06 cm² vs. 0.33 ± 0.12 cm², $p < 0.01$), whereas MR degree in the control group progressed to moderate to severe at sacrifice. At sacrifice, MR severity in the PVA group was significantly lower than that in the control group (VC width: 0.17 ± 0.08 cm vs. 0.60 ± 0.14 cm, $p < 0.001$; VC area: 0.06 ± 0.06 cm² vs. 0.50 ± 0.30 cm², $p < 0.01$). Figure 4 shows trace MR in a PVA-treated sheep versus moderate to severe MR in a control sheep 8 weeks after injection. (Figure 4A corresponds to Online Video 1; Figure 4B corresponds to Online Video 2; Figure 4C corresponds to Online Video 3; Figure 4D corresponds to Online Video 4).

LV AND LA REMODELING

LV and LA remodeling over time in both groups are demonstrated in Figure 5. LV volumes increased significantly from baseline to the chronic MR stage with a significant decrease in EF in both groups (all $p < 0.001$). LV volumes, EF, and LA volume were comparable between the 2 groups at baseline and at the chronic MR stage. At 8 weeks after PVA injection, compared with the chronic MR stage, there was no continued increase in EDV or ESV (EDV: 72.6 ± 15.3 ml vs. 72.7 ± 13.9 ml; ESV: 41.1 ± 10.4 ml vs. 41.0 ± 9.3 ml; both $p > 0.05$) and EF remained stable (EF: $43.6 \pm 4.6\%$ vs. $43.8 \pm 3.4\%$, $p > 0.05$). Additionally, LA volume decreased significantly (29.9 ± 6.7 ml vs. 35.7 ± 5.3 ml, $p = 0.05$) after PVA injection. In contrast, at 8 weeks after saline injection, LV and LA volumes continued to increase significantly (EDV: 91.2 ± 18.0 ml vs. 68.9 ± 19.2 ml; ESV: 55.9 ± 12.4 ml vs. 40.0 ± 14.5 ml; LA volume: 51.3 ± 4.9 ml vs. 38.1 ± 7.2 ml, all $p < 0.05$). At sacrifice, compared with the control group, the PVA group had significantly lower LV and LA volumes (EDV: 72.6 ± 15.3 ml vs. 91.2 ± 18.0 ml, $p < 0.05$; ESV: 41.1 ± 10.4 ml vs. 55.9 ± 12.4 ml; $p <$

0.05; LA volume: 29.9 ± 6.7 ml vs. 51.3 ± 4.9 ml, $p < 0.001$) and better LV systolic function (EF: $43.6 \pm 4.6\%$ vs. $38.9 \pm 3.7\%$, $p = 0.05$).

3D MITRAL VALVE GEOMETRY

Table 1 demonstrates mitral valve geometry over time in both groups assessed by 3D echocardiography. Mitral annular area, leaflet closure area, tenting volume, tethering length, and IPMD increased significantly from baseline to the chronic MR stage in both groups. Parameters of mitral valve geometry were comparable between the 2 groups at the chronic MR stage. At 8 weeks after PVA injection, favorable changes were found in the PVA group, with significant decreases in mitral annular area, leaflet closure area, IPMD, and tenting volume. In contrast, at 8 weeks after saline injection, IPMD and tenting volume continued to increase significantly with the tendency toward increase in mitral annular area, leaflet closure area, and tethering length in the control group. At sacrifice, the control group, compared with the PVA group, exhibited significantly greater mitral annular area, leaflet closure area, tethering length, IPMD, and tenting volume.

ELECTROCARDIOGRAPHIC AND HEMODYNAMIC DATA

During PVA or saline injection, there were no ischemic electrocardiographic changes or arrhythmias. Eight sheep in the PVA group and 6 sheep in the control group had adequate tracing quality for data analysis. From chronic MR stage to 8 weeks after PVA injection, hemodynamic data remained stable (Table 2). In contrast, at 8 weeks after saline injection, there was a reduction in elastance and minimum first derivative of pressure measured over time whereas there was an increase in tau in the control group. However, no statistically significant difference was found between groups at the chronic MR stage and at sacrifice.

PVA MORPHOLOGY AND HISTOLOGY

Gross anatomical examination showed solidified PVA gel encapsulated within the posterior-lateral wall surrounded by scar tissue and there was no evidence of polymer erosion to or through the endo- or epicardial surfaces (Figure 6). The histology examination showed encapsulated PVA polymer surrounded by infarcted myocardium and dense scarring. There was evidence of expected foreign body giant cell reaction locally at the PVA-scar interface, typically seen in reaction to presence of implanted foreign materials (15). No systemic embolus was found in the brain, spleen, or kidney.

DISCUSSION

The main results of this study are as follow: 1) injection of PVA into infarcted myocardium is effective in treating IMR over 8 weeks of follow-up; 2) this technique stabilizes the mitral-LV complex by correcting leaflet tethering and restoring effective coaptation; and 3) chronic PVA application attenuates continued LV remodeling in a chronic IMR model.

PERSISTENT MR REDUCTION

The present data demonstrate that PVA injection acutely reduces IMR, and more importantly, this favorable effect persists over 8 weeks without MR recurrence. Other evidence of chronic efficacy of PVA injection on MR reduction is supported by LA reverse

remodeling. Analysis of mitral valve geometry by 3D echocardiography confirms that PVA injection attenuates leaflet tethering and improves leaflet coaptation geometry over 8 weeks after injection. Our results suggest that chronic efficacy of PVA injection in persistent MR reduction is associated with structural stabilization of the mitral-LV complex by correcting the mitral leaflet tethering and restoring the coaptation. The mechanism of structural stabilization by PVA may relate to buttressing of the infarcted wall and preventing its bulging. The result that PVA injection acutely reduces MR in an acute IMR model also supports an acute and favorable PM repositioning and reduction in infarct bulging from PVA injection as a mechanism for MR reduction (10).

EFFECT ON LV REMODELING

Preventing or attenuating LV remodeling has been considered a primary target for post-MI treatment. The present study showed that overall EDV, ESV, and EF stabilized chronically after PVA injection, whereas these benefits were not observed in the sham-operated control subjects. The favorable effect on stabilization of LV remodeling and function may relate to reduction of IMR. Reduction of IMR decreases the volume overload and stress on the LV and might subsequently attenuate the continued LV remodeling process. Beeri et al. (16) showed that IMR can potentially exacerbate LV remodeling in a vicious cycle. Early repair of moderate MR in the setting of apical MI substantially reverses progressive remodeling process (17). Similarly, Messas et al. (18) reported chordal cutting diminished MR in the chronic IMR setting and limited the LV remodeling seen in control subjects. However, discrepancies still exist regarding the effect of elimination of IMR on LV remodeling (19,20). Guy et al. (20) demonstrated in a sheep model that prevention of LV remodeling and infarct expansion was achieved by prophylactic ventricular restraint, not by ring annuloplasty, even though both procedures decreased IMR. Thus, another potential mechanism for limiting LV remodeling might relate to constraint of the infarcted myocardium by locally applied PVA. Restraint of infarct expansion using an external patch preserved both LV geometry and cardiac function (9). LV restraint could also be achieved less invasively by direct injection of biomaterials, such as fibrin, collagen, or alginate hydrogel into the infarcted zone to reshape and buttress the bulging LV (21,22). Studies have shown that injection of biomaterials replaces damaged extracellular matrix and thickens the infarcted wall. By thickening the damaged area, wall stress is decreased, and subsequently reduces the paradoxical motion caused by infarct thinning and limits the adverse LV remodeling and dysfunction. Wall et al. (23) confirmed this benefit in a computer modeling study, showing that implanting noncontractile materials into damaged myocardium can decrease end-systolic fiber stress. Moreover, the injection resulted in the improvement of EF and stroke volume-EDV relationship. An advantage of PVA hydrogel is that it forms a stable, nondegradable, inert gel, making it ideal for chronic use. Ifkovits et al. (24) were the first to explore the effects of the mechanical properties of injectable materials on post-MI LV remodeling. They found injection of higher mechanical modulus hydrogel (43 kPa) in an ovine model limited the infarct expansion, prevented LV remodeling, and improved cardiac function when compared with lower modulus hydrogel (8 kPa) in an infarct control group (24). This is evidence that hydrogel injection attenuates LV remodeling, which depends on hydrogel mechanics, and the higher modulus hydrogel is better able to stabilize the myocardium. The PVA polymer used in the present study has a similarly high mechanical

modulus, which solidifies at body temperature after injection and forms a hard substance localized within the infarct zone acting as an internal stiffener or tissue-bulking agent.

In our study, although the overall EDV and ESV did not change significantly, 8 weeks after PVA injection, mild continued LV remodeling was noted in 3 animals. This is similar to the clinically observed variability in extent of remodeling or wall bulging among patients with a comparable inferoposterior MI territory. Considering that PVA is locally applied, global LV remodeling would still be expected to progress in the border zone or remote area. In contrast, significant continued LV remodeling was observed in all the control animals, which might be attributable to both persistent MR and infarct expansion.

CLINICAL IMPLICATIONS

Injection of PVA hydrogel into infarcted myocardium is a novel comprehensive approach to treating IMR by specifically targeting its causative mechanism in the beating heart. Compared with surgical ring annuloplasty, PVA injection offers an alternative therapy for treating IMR that directly addresses the LV distortion and tethering mechanism. Recently, percutaneous mitral valve repair MitraClip (Abbott, Abbott Park, Illinois) has been approved for degenerative mitral valve disease and is currently undergoing a clinical trial to assess efficacy in functional MR (25). Importantly, PVA injection might add to current therapies for IMR and may prove useful as a stand-alone therapy for IMR or in conjunction with ring annuloplasty or MitraClip therapy.

Additionally, a fundamental limitation of ring annuloplasty is a significant recurrence rate of IMR that results from persistent leaflet tethering in the setting of continued LV remodeling. Injection of PVA hydrogel into the infarcted myocardium over the PM has the potential to both reduce MR by decreasing leaflet tethering but also to stabilize LV geometry and attenuate adverse LV remodeling by acting as an internal constraint. This present study demonstrates that localized PVA injection has prolonged efficacy with chronic follow-up after injection into the heart with a chronically remodeled MI. These results provide important insights and suggest the potential clinical application of a new therapeutic approach in patients with IMR. At this stage, injection of PVA is performed via thoracotomy, but is less invasive than other surgical strategies that target the LV distortion or leaflet tethering, such as infarct plication or surgical relocation of the PM. Development of a catheter-based approach would hold promise for future minimally invasive percutaneous delivery and injection. Devices to stabilize the needle system platform against the myocardium and syringes with set PVA volumes to standardize delivery volumes can be adopted for percutaneous injection.

STUDY LIMITATIONS

First, several factors including the size of infarction, sites of injection, and amount of polymer injected potentially contribute to the efficacy of this treatment. These variables may limit the results in clinical investigation. Second, due to the data variations, this study might be underpowered to demonstrate the hemodynamic benefit of the PVA group over the control group at sacrifice. Third, the model of the present experiment is an asymmetric tethering model resulting from posterolateral MI, the most clinically relevant scenario. The

benefits of PVA injection can also be studied in the future for more extensive myocardial infarction involving both PM or the anterior wall, with potentially prominent annular dilation. Fourth, the beneficial effects were observed over 8 weeks after the injection of PVA. Future investigation can explore longer time periods to evaluate the durability of this procedure, as late adverse remodeling after ring annuloplasty with recurrent MR is frequently seen years after the procedure, but the timing used enabled demonstration of maintained reduction of MR and tethering.

CONCLUSIONS

Chronic polymer injection in a chronic IMR model results in persistent reduction of MR and attenuation of continued LV remodeling over 8 weeks of follow-up. This suggests an alternative approach to the treatment of IMR with maintained efficacy over time.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The authors thank Dr. David Sho-Chao Hung for his editorial assistance.

This work was supported in part by a grant #R01 HL092101 from the National Institutes of Health/National Heart, Lung, and Blood Institute(Dr. Hung); the Echo-Investigator Award from the American Society of Echocardiography (Dr. Hung); grants #R01 HL109506 and #K24 HL67434 from National Institutes of Health/National Heart, Lung, and Blood Institute (Dr. Levine); and grant #07CVD04 from the Leducq Foundation (Dr. Levine). Dr. Braithwaite is an employee and shareholder of Cambridge Polymer Inc. Dr. Muratoglu has an equity interest in Cambridge Polymer Inc.; has received royalties from Zimmer, Biomet, Corin, Iconacy, Renovis, Conformis, Aston Medical, Meril Healthcare, Arthrex, Mako, Ceramtec; has received research support from Biomet, Mako, and Depuy; and has received or materials support from Biomet, Orthopaedic Technology Group.

ABBREVIATIONS AND ACRONYMS

2D	2-dimensional
3D	3-dimensional
EDV	end-diastolic volume
EF	ejection fraction
ESV	end-systolic volume
IMR	ischemic mitral regurgitation
IPMD	interpapillary muscle distance
LA	left atrial
LV	left ventricular
MI	myocardial infarction
MR	mitral regurgitation

PM	papillary muscle
PVA	polyvinyl alcohol
VC	vena contracta

References

1. Bursi F, Enriquez-Sarano M, Nkomo VT, et al. Heart failure and death after myocardial infarction in the community: the emerging role of mitral regurgitation. *Circulation*. 2005; 111:295–301. [PubMed: 15655133]
2. Perez de Isla L, Zamorano J, Quezada M, et al. Prognostic significance of functional mitral regurgitation after a first non-ST-segment elevation acute coronary syndrome. *Eur Heart J*. 2006; 27:2655–60. [PubMed: 17015403]
3. Grigioni F, Enriquez-Sarano M, Zehr KJ, Bailey KR, Tajik AJ. Ischemic mitral regurgitation: long-term outcome and prognostic implications with quantitative Doppler assessment. *Circulation*. 2001; 103:1759–64. [PubMed: 11282907]
4. Koelling TM, Aaronson KD, Cody RJ, Bach DS, Armstrong WF. Prognostic significance of mitral regurgitation and tricuspid regurgitation in patients with left ventricular systolic dysfunction. *Am Heart J*. 2002; 144:524–9. [PubMed: 12228791]
5. Nishimura RA, Otto CM, Bonow RO, et al. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2014; 63:e57–185. [PubMed: 24603191]
6. Magne J, Sénéchal M, Dumesnil JG, Pibarot P. Ischemic mitral regurgitation: a complex multifaceted disease. *Cardiology*. 2009; 112:244–59. [PubMed: 18758181]
7. Hung J, Papakostas L, Tahta SA, et al. Mechanism of recurrent ischemic mitral regurgitation after annuloplasty: continued LV remodeling as a moving target. *Circulation*. 2004; 110(Suppl 1):II85–90. [PubMed: 15364844]
8. Kuwahara E, Otsuji Y, Iguro Y, et al. Mechanism of recurrent/persistent ischemic/functional mitral regurgitation in the chronic phase after surgical annuloplasty: importance of augmented posterior leaflet tethering. *Circulation*. 2006; 114(Suppl 1):I529–34. [PubMed: 16820632]
9. Hung J, Chaput M, Guerrero JL, et al. Persistent reduction of ischemic mitral regurgitation by papillary muscle repositioning: structural stabilization of the papillary muscle-ventricular wall complex. *Circulation*. 2007; 116(Suppl 11):I259–63. [PubMed: 17846314]
10. Hung J, Solis J, Guerrero JL, et al. A novel approach for reducing ischemic mitral regurgitation by injection of a polymer to reverse remodel and reposition displaced papillary muscles. *Circulation*. 2008; 118(Suppl 14):S263–9. [PubMed: 18824765]
11. Solis J, Levine RA, Johnson B, et al. Polymer injection therapy to reverse remodel the papillary muscles: efficacy in reducing mitral regurgitation in a chronic ischemic model. *Circ Cardiovasc Interv*. 2010; 3:499–505. [PubMed: 20736444]
12. Llaneras MR, Nance ML, Streicher JT, et al. Large animal model of ischemic mitral regurgitation. *Ann Thorac Surg*. 1994; 57:432–9. [PubMed: 8311608]
13. Zeng X, Levine RA, Hua L, et al. Diagnostic value of vena contracta area in the quantification of mitral regurgitation severity by color Doppler 3D echocardiography. *Circ Cardiovasc Imaging*. 2011; 4:506–13. [PubMed: 21730026]
14. Chaput M, Handschumacher MD, Tournoux F, et al. Mitral leaflet adaptation to ventricular remodeling: occurrence and adequacy in patients with functional mitral regurgitation. *Circulation*. 2008; 118:845–52. [PubMed: 18678770]
15. Della Barbera M, Laborde F, Thiene G, et al. Sovering annuloplasty rings: experimental pathology in the sheep model. *Cardiovasc Pathol*. 2005; 14:96–103. [PubMed: 15780801]
16. Beerli R, Yosefy C, Guerrero JL, et al. Mitral regurgitation augments post-myocardial infarction remodeling failure of hypertrophic compensation. *J Am Coll Cardiol*. 2008; 51:476–86. [PubMed: 18222360]

17. Beeri R, Yosefy C, Guerrero JL, et al. Early repair of moderate ischemic mitral regurgitation reverses left ventricular remodeling: a functional and molecular study. *Circulation*. 2007; 116(Suppl 11):I288–93. [PubMed: 17846319]
18. Messas E, Bel A, Szymanski C, et al. Relief of mitral leaflet tethering following chronic myocardial infarction by chordal cutting diminishes left ventricular remodeling. *Circ Cardiovasc Imaging*. 2010; 3:679–86. [PubMed: 20826595]
19. Matsuzaki K, Morita M, Hamamoto H, et al. Elimination of ischemic mitral regurgitation does not alter long-term left ventricular remodeling in the ovine model. *Ann Thorac Surg*. 2010; 90:788–94. [PubMed: 20732497]
20. Guy TS 4th, Moainie SL, Gorman JH 3rd, et al. Prevention of ischemic mitral regurgitation does not influence the outcome of remodeling after posterolateral myocardial infarction. *J Am Coll Cardiol*. 2004; 43:377–83. [PubMed: 15013117]
21. Mukherjee R, Zavadzkas JA, Saunders SM, et al. Targeted myocardial microinjections of a biocomposite material reduces infarct expansion in pigs. *Ann Thorac Surg*. 2008; 86:1268–76. [PubMed: 18805174]
22. Dai W, Wold LE, Dow JS, Kloner RA. Thickening of the infarcted wall by collagen injection improves left ventricular function in rats: a novel approach to preserve cardiac function after myocardial infarction. *J Am Coll Cardiol*. 2005; 46:714–9. [PubMed: 16098441]
23. Wall ST, Walker JC, Healy KE, Ratcliffe MB, Guccione JM. Theoretical impact of the injection of material into the myocardium: a finite element model simulation. *Circulation*. 2006; 114:2627–35. [PubMed: 17130342]
24. Ifkovits JL, Tous E, Minakawa M, et al. Injectable hydrogel properties influence infarct expansion and extent of postinfarction left ventricular remodeling in an ovine model. *Proc Natl Acad Sci U S A*. 2010; 107:11507–12. [PubMed: 20534527]
25. [Accessed December 18, 2014] Cardiovascular outcomes assessment of the MitraClip therapy percutaneous therapy for high surgical risk patients (COAPT). Available at: <http://clinicaltrials.gov/ct2/show/NCT01626079>

FIGURE 1. Study Design

Posterolateral myocardial infarction (MI) was induced by ligation of circumflex marginal branches in sheep. Chronic ischemic mitral regurgitation (MR) was developed 8 weeks after infarction. Animals were then divided into polyvinyl-alcohol (PVA) injection and control groups. Eight weeks after injection, the animals were sacrificed. Echocardiography was performed at baseline, prior to injection, and 8 weeks after injection.

FIGURE 2. Schematic of PVA Injection

Schematic of PVA injection into infarcted myocardium underlying papillary muscle (PM) to attenuate leaflets tethering and reduce MR. AO = aorta; other abbreviation as in Figure 1.

FIGURE 3. MR Reduction

Comparisons of MR reduction assessed by vena contracta width (**A**) and vena contracta area (**B**) between the PVA and control groups. Abbreviations as in Figure 1.

FIGURE 4. MR Reduction

Chronic PVA application results in persistent MR reduction in a PVA animal (A, B, also see Online Videos 1 and 2). In contrast, no beneficial effect on MR reduction was found 8 weeks after saline injection in a control sheep (C, D, also see Online Videos 3 and 4).

Abbreviations as in Figure 1.

FIGURE 5. LV and LA Remodeling

Comparisons of left ventricular (LV) and left atrial (LA) volumes at all stages between the PVA group and untreated control group. EDV = end-diastolic volume; EF = ejection fraction; ESV = end-systolic volume; other abbreviations as in Figure 1.

FIGURE 6. PVA Morphology

Gross appearance of polyvinyl-alcohol (PVA) polymer (**white oval**) injected into chronic infarction for over 8 weeks.

TABLE 1

Comparison of Mitral Valve Geometry Between Groups

	PVA Group			Control Group		
	Baseline	Chronic MR	Sacrifice	Baseline	Chronic MR	Sacrifice
Mitral annular area, cm ²	7.87 ± 1.10	9.44 ± 1.41 [*]	8.31 ± 0.82 ^{‡‡}	8.19 ± 1.21	10.53 ± 0.89 [*]	12.18 ± 2.20
Leaflet closure area, cm ²	8.72 ± 1.14	11.15 ± 1.52 [*]	9.64 ± 0.84 ^{‡‡}	9.20 ± 1.15	12.13 ± 0.89 [*]	13.88 ± 2.20
Tethering length, mm	27.3 ± 2.54	32.41 ± 2.30 [*]	30.48 ± 3.09 [§]	28.04 ± 2.04	32.82 ± 3.11 ^{//}	34.55 ± 3.29
Interpapillary muscles distance, mm	19.56 ± 3.40	25.57 ± 2.77 [*]	21.80 ± 3.39 ^{‡§}	17.91 ± 3.16	23.70 ± 3.67	26.70 ± 4.16 [†]
Tenting volume, ml	0.96 ± 0.19	1.78 ± 0.61 [*]	1.42 ± 0.44 ^{§//}	0.91 ± 0.21	1.56 ± 0.08 [*]	2.04 ± 0.30 ^{//}

Values are mean ± SD.

- ^{*} p < 0.01 vs. baseline of the same group.
 - [†] p < 0.01 vs. chronic MR stage of the same group.
 - [‡] p < 0.01 vs. control group at sacrifice.
 - [§] p < 0.05 vs. control group at sacrifice.
 - ^{//} p < 0.05 vs. baseline of the same group.
 - [¶] p < 0.05 vs. chronic MR stage of the same group.
- MR = mitral regurgitation; PVA = polyvinyl-alcohol.

TABLE 2**Hemodynamic Data**

	PVA Group		Control Group	
	Chronic MR	Sacrifice	Chronic MR	Sacrifice
Heart rate, beats/min	93 ± 11	102 ± 15	89 ± 13	90 ± 9
ESP, mm Hg	80 ± 7	76 ± 10	79 ± 10	78 ± 11
EDP, mm Hg	17 ± 6	13 ± 4	16 ± 4	18 ± 6
dP/dt _{max} , mm Hg/s	1,519 ± 489	1,589 ± 680	1,292 ± 327	1,188 ± 183
dP/dt _{min} , mm Hg/s	-1,138 ± 215	-1,014 ± 257	-1,082 ± 159	-776 ± 209 *
Relaxation constant, ms	51 ± 11	57 ± 19	53 ± 5	70 ± 19
Elastance, mm Hg/ml	3.0 ± 1.2	2.8 ± 0.9	3.2 ± 1.4	2.6 ± 1.1 *
Stiffness	0.022 ± 0.017	0.014 ± 0.011	0.027 ± 0.01	0.015 ± 0.011
PRSW slope	48 ± 16	57 ± 33	50 ± 9	37 ± 15

Values are mean ± SD.

* p < 0.05, sacrifice vs. chronic MR stage in the control group.

dP/dt = first derivative of pressure measured over time; EDP = end-diastolic pressure; ESP = end-systolic pressure; MR = mitral regurgitation; PRSW = pre-load recruited stroke work; PVA = polyvinyl-alcohol.