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TRANSLATIONAL

Efficacy of Polymer Injection for Ischemic Mitral Regurgitation

Persistent Reduction of Mitral Regurgitation and Attenuation of Left Ventricular Remodeling

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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 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. (J Am Coll Cardiol Intv 2015;8:355-63) © 2015 by the American College of Cardiology Foundation.

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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

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.

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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