Application of polymer-mesh device to remodel left ventricular–mitral valve apparatus in ischemic mitral regurgitation

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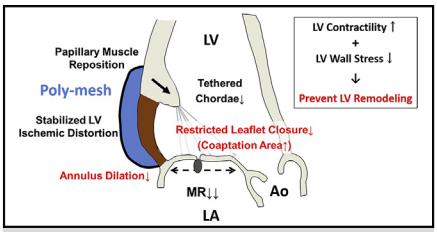
ABSTRACT

Objectives: Ischemic mitral regurgitation (IMR) results from ischemic left ventricular (LV) distortion and remodeling, which displaces the papillary muscles and tethers the mitral valve leaflets apically. The aim of this experimental study was to examine efficacy of an adjustable novel polymer filled mesh (poly-mesh) device to reverse LV remodeling and reduce IMR.

Methods: Acute (N = 8) and chronic (8 weeks; N = 5) sheep models of IMR were studied. IMR was produced by ligation of circumflex branches to create myocardial infarction. An adjustable poly-mesh device was attached to infarcted myocardium in acute and chronic IMR models and compared with untreated sham sheep. Two- and 3-dimensional echocardiography and hemodynamic measurements were performed at baseline, post IMR, and post poly-mesh (humanely killed).

Results: In acute models, moderate IMR developed in all sheep and decreased to trace/mild (vena contracta: 0.50 ± 0.09 cm to 0.26 ± 0.12 cm; $P < .01$) after poly-mesh. In chronic models, IMR decreased in all sheep after poly-mesh, and this reduction persisted over 8 weeks (vena contracta: 0.42 ± 0.09 cm to 0.08 ± 0.12 cm; $P < .01$) with significant increase in the slope of end-systolic pressure–volume relationship (1.1 ± 0.5 mm Hg/mL to 2.9 ± 0.7 mm Hg/mL; $P < .05$). There was a significant reduction in LV volumes from chronic IMR to euthanasia stage with poly-mesh compared with sham group (%end-diastolic volume change −20 ± 11 vs 15% ± 16%, $P < .01$; %end-systolic volume change −14% ± 19% vs 22% ± 22%, $P < .05$; poly-mesh vs sham group) consistent with reverse remodeling.

Conclusions: An adjustable polymer filled mesh device reduces IMR and prevents continued LV remodeling during chronic follow-up. (J Thorac Cardiovasc Surg 2017;■:1-9)



Poly-mesh device for relieving leaflet tethering and MR and prevention of LV remodeling.

Central Message

This study examines the efficacy of a novel therapy for ischemic mitral regurgitation that directly relieves leaflet tethering while also preventing the progression of both LV and LA adverse remodeling.

Perspective

This study demonstrates the chronic efficacy of a novel therapy for IMR that both reduces MR but also results in stabilization and repositioning of the infarcted myocardial wall. This approach offers a potential alternative for relieving tethering and IMR and prevention of progression of both LV and LA adverse remodeling, and furthermore it has potential minimally invasive applications in the beating heart.

See Editorial Commentary page XXX.

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Ischemic mitral regurgitation (IMR) is an important consequence of myocardial infarction (MI) and associated with increased mortality and morbidity. IMR results from ischemic left ventricular (LV) distortion, which displaces the papillary muscles (PMs) and tethers the mitral valve (MV) leaflets apically, restricting leaflets closure and dilating the mitral annulus.[1] Therapy for IMR remains controversial and challenging.[2,3] Mitral ring annuloplasty, a popular surgical therapy for IMR, is associated with a

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This work was supported in part by National Institutes of Health (NIH)/The National Heart, Lung, and Blood Institute (NHLBI) R01 HL092101 and by Echo-Investigator Award from American Society of Echocardiography (to Dr Hung), and by grants NIH/NHLBI R01 038176 (to Dr Levine), and grants Overseas Research Fellowship Award from Japanese Society of Echocardiography and Research Fellowship Award from Uehara Memorial Foundation, Tokyo, Japan (to Dr Kataoka).

Received for publication April 5, 2017; revisions received Oct 14, 2017; accepted for publication Nov 5, 2017.

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0022-5223/$36.00

https://doi.org/10.1016/j.jtcvs.2017.11.006

Abbreviations and Acronyms

2D = 2-dimensional
3D = 3-dimensional
dP/dt = rate of rise of left ventricular pressure
EDV = end-diastolic volume
Emax = slope of end-systolic pressure–volume relationship
ESV = end-systolic volume
GLS = global longitudinal strain
IMR = ischemic mitral regurgitation
LA = left atrium
LV = left ventricular
LVEF = left ventricular ejection fraction
MI = myocardial infarction
MR = mitral regurgitation
MV = mitral valve
PISA = proximal isovelocity surface area
PM = papillary muscle
poly-mesh = polymer-filled mesh
WMSI = wall motion score index

significant recurrence rate of IMR and has not been effective at reducing LV adverse remodeling.[4-6] Mitral ring annuloplasty also does not directly address the fundamental mechanistic cause of IMR, which is LV distortion resulting in mitral leaflet tethering.

To directly address ischemic LV morphology and to prevent further LV adverse remodeling, we developed and examined the efficacy of a biocompatible polymer-filled mesh (poly-mesh) device for treatment of IMR. Our group has previously described 2 strategies to alleviate IMR: direct polymer injection into the infarcted ventricular territory to reposition the PM and a patch balloon device to externally remodel the infarcted ventricular segment.[7,8] The poly-mesh device combines these 2 latter therapies by using biocompatible polymers that can be adjusted to optimize displacement and position while being contained within mesh for constraint of LV adverse remodeling.[7,8] This results in a device that can be tailored to patient-specific LV and MV remodeling changes, as it can be adjusted, resized, and controlled to achieve the desired levels of reverse remodeling in an infarcted and distorted LV myocardium. We assessed this poly-mesh device initially in an acute IMR model to test proof of concept and subsequently in a chronic IMR model, as the latter is the more commonly encountered clinical situation.

METHODS

Operation and Study Design

Acute and chronic IMR models were produced via an established ovine model.[7-9] This study was reviewed and approved by the institutional Animal Care Committee (institutional review board information: institutional protocol number; 2012N000160/2, approval date; March 14, 2013). The heart was exposed through a left thoracotomy and animals monitored with blood pressure, electrocardiogram, and oxygen saturation throughout the procedures. For acute IMR, the inferoposterior wall of the LV was infarcted by ligating the second, third left circumflex obtuse marginal branches, and posterior descending artery. Echocardiographic imaging confirmed the development of at least moderate IMR. The poly-mesh device was then attached to the surface of the infarcted LV epicardium with sutures followed by staples via a SECURESTRAP staple-gun (ETHICON LLC, Guaynabo, Puerto Rico) under echocardiographic guidance (Figure 1, *left*) and saline was applied directly to the surface of the device to hydrate the hydrogel, which was allowed to swell for approximately 10 minutes (Figure 1, *right*, and Video 1). The poly-mesh device can be adjusted intraoperatively to optimize IMR reduction by adding extra polymer granules through a 25-gauge needle.

Hemodynamic measurements were acquired with a microcatheter placed in the LV, and LV pressure was recorded along with an electrocardiogram lead on a physiological recorder (iWorx Systems Inc, Dover, NH). Two-dimensional (2D) and 3-dimensional (3D) epicardial echocardiographic images were obtained (iE33, X3 matrix; Philips Medical Systems, Andover, Mass). Echo data acquisition was performed as described previously.[7,8]

Eight sheep (mean 6.9 ± 1.0 months, 4 males, 40.6 ± 1.9 kg) were in the acute experiments. Data were collected in 3 stages as follows: baseline, acute IMR (within 1 hour after the IMR creation), and acute poly-mesh (within 1 hour of attachment) (Figure 2, *upper panel*). For chronic IMR, after MI creation, the chest was closed, and the 10 sheep were allowed to recover. Following 8 weeks of LV remodeling, 5 sheep (mean 7.8 ± 2.4 month at baseline, 2 males, mean 42.0 ± 3.3 kg at baseline) underwent a second thoracotomy, and poly-mesh was applied chronically for an additional 8 weeks before they were euthanized. In addition, 5 sham sheep (mean 5.4 ± 1.3 month at baseline, 3 males, mean 43.4 ± 3.0 kg at baseline) underwent the same surgeries but did not have a poly-mesh device placed. There were no significant differences in the characteristics between the poly-mesh and sham sheep. In the chronic experiments, data were collected at baseline, chronic IMR stage (before attachment), and euthanasia stage (chronic poly-mesh) stages; (Figure 2, *lower panel*).

Poly-Mesh Device

The device used to create postinfarction LV myocardial displacement was a hybrid construct composed of an expandable hydrogel confined within a porous mesh (Cambridge Polymer Group, Inc, Boston, Mass). Each device was composed of either highly absorbent dehydrated polyacrylate (acute IMR models) or polyacrylamide granules (chronic IMR models) contained within 2 confining layers of a porous polyester mesh and surrounded by a thinner outer border of reinforcing polyester fabric (Figure 1). The device was intended to be delivered in a compact form (less than 1 cm maximum diameter) and then rapidly expand once anchored to the heart wall and hydrated with saline.

Polyacrylamide has been used successfully in tissue bulking, reconstructive applications, urinary incontinence, and soft contact lenses.[10-12] Polyester such as polyethylene terephthalate, or PET, are used frequently in biomedical materials.[13] Of note, the exact polymer material chosen for the mesh is not critical for this device, and other chemistries may be suitable. The hydrogel patch devices were sterilized by electron beam radiation at a dose of 32.5 kGy ± 2.5 kGy before use in chronic IMR models. Cytotoxicity testing (per ISO 10993-5 MEM Elution Method) found a Grade 0 reactivity level for both the dehydrated polyacrylamide granules and the polyester mesh. Endotoxicity testing (per USP <85> LAL kinetic-chromogenic method) found a reactivity of less than 0.975 EU/g for the polyacrylamide granules and less than 0.004 EU/cm^2 for the polyester mesh.