Biodegradable elastic patch plasty ameliorates left ventricular adverse remodeling after ischemia–reperfusion injury: A preclinical study of a porous polyurethane material in a porcine model

Ryotaro Hashizume, MD, PhD,[a] Kazuro L. Fujimoto, MD, PhD,[a] Yi Hong, PhD,[a] Jianjun Guan, PhD,[a] Catalin Toma, MD,[b] Kimimasa Tobita, MD,[a,c] and William R. Wagner, PhD[a,d]

Objective: Myocardial infarction (MI) can lead to irreversible adverse left ventricular remodeling resulting in subsequent severe dysfunction. The objective of this study was to investigate the potential for biodegradable, elastomeric patch implantation to positively alter the remodeling process after MI in a porcine model.

Methods: Yorkshire pigs underwent a 60-minute catheter balloon occlusion of the left circumflex artery. Two weeks after MI animals underwent epicardial placement of a biodegradable, porous polyurethane (poly(ester urethane)urea; PEUU) patch (MI+PEUU, n = 7) or sham surgery (MI+sham, n = 8). Echocardiography before surgery and at 4 and 8 weeks after surgery measured the end-diastolic area (EDA) and fractional area change (% FAC). All animals were humanely killed 8 weeks after surgery and hearts were histologically assessed.

Results: At 8 weeks, echocardiography revealed greater EDA values in the MI+sham group (23.6 ± 6.6 cm^2, mean ± standard deviaation) than in the MI+PEUU group (15.9 ± 2.5 cm^2) ($P < .05$) and a lower %FAC in the MI+sham group (24.8 ± 7.6) than in the MI+PEUU group (35.9 ± 7.8) ($P < .05$). The infarcted ventricular wall was thicker in the MI+PEUU group (1.56 ± 0.5 cm) than in the MI+sham group (0.91 ± 0.24 cm) ($P < .01$).

Conclusions: Biodegradable elastomeric PEUU patch implantation onto the porcine heart 2 weeks post-MI attenuated left ventricular adverse remodeling and functional deterioration and was accompanied by increased neovascularization. These findings, although limited to a 2-month follow-up, may suggest an attractive clinical option to moderate post-MI cardiac failure. (J Thorac Cardiovasc Surg 2013;146:391-9)

Video clip is available online.

Supplemental material is available online.

Myocardial infarction (MI) is the most frequently identified specific cause of dilated cardiomyopathy, leading to symptomatic congestive heart failure over time. Regional structural changes in left ventricular (LV) remodeling after MI can lead to global LV geometric change, which contributes to an increase in LV wall stress[1] and mitral regurgitation.[2] Epidemiologically, survival after MI is related to the magnitude of LV dilatation.[3] Thus, therapies designed to attenuate postinfarct LV dilatation, by pharmacologic or surgical means, have been pursued to alleviate postinfarction morbidity and mortality in adverse remodeling after MI.

A spectrum of surgical procedures, cardiac resynchronization therapy (biventricular pacing),[4] or pharmacologic therapy (eg, angiotensin-converting enzyme inhibitors and beta-blockers)[5] have been applied in the clinical setting after MI in an effort to limit adverse LV remodeling. Surgical approaches include surgical ventricular restoration with an endocardial patch such as the Dor procedure[6] or ventricular wrapping with an epicardial patch.[7] The patches used in these procedures, however, have been made from nonbiodegradable materials with low elasticity. Such materials raise concerns about a chronic foreign-body response, potentially leading to difficulties in reoperation, or LV diastolic failure owing to nonelastic encapsulation. Microbial infection is also a concern that arises when implanting a permanent foreign body.

In animal models for ischemic cardiomyopathy, a variety of biodegradable materials as interventional therapeutic strategies have been investigated, including epicardial patches with and without cellular constituents,[8-12] intramyocardial

From the McGowan Institute for Regenerative Medicine,[a] University of Pittsburgh; the University of Pittsburgh Medical Center,[b] Cardiovascular Institute; the Department of Developmental Biology,[c] University of Pittsburgh; and the Departments of Bioengineering and Chemical Engineering,[d] University of Pittsburgh, Pittsburgh, Pa.

Funded by the National Heart, Lung and Blood Institute, National Institutes of Health grant HL069368.

Disclosures: Authors have nothing to disclose with regard to commercial support.

R.H. and K.L.F. contributed equally to this work.

Present addresses: R.H: Department of Pathology and Matrix Biology, Mie University Graduate School of Medicine, Tsu, Mie, Japan; J.G: Department of Materials Science and Engineering, The Ohio State University, Columbus, Ohio.

Received for publication July 2, 2012; revisions received Oct 6, 2012; accepted for publication Nov 6, 2012; available ahead of print Dec 10, 2012.

Address for reprints: William R. Wagner, PhD, Bridgeside Point II, 450 Technology Dr, Suite 300, Pittsburgh, PA 15219 (E-mail: wagnerwr@upmc.edu).

0022-5223/$36.00

http://dx.doi.org/10.1016/j.jtcvs.2012.11.013

Abbreviations and Acronyms

αSMA = α-smooth muscle actin
EDA = end-diastolic area
EF = ejection fraction
ESA = end-systolic area
%FAC = fractional area change
LV = left ventricular (ventricle)
LVEDV = left ventricular end-diastolic volume
LVESV = left ventricular end-systolic volume
MI = myocardial infarction
PEUU = poly(ester urethane)urea

hydrogel injectables,[13,14] and intracoronary injectables.[15] We have previously reported that an elastic, biodegradable cardiac patch, without cells, prevents cardiac remodeling and improves LV function after MI with a rodent model.[8] However, whether this relatively straightforward approach would serve to similarly prevent LV remodeling in a more clinically relevant large animal model has not been addressed. Namely, the efficacy of epicardial patch plasty with a degradable material in a large animal model has not been addressed to date. Our objective here was to examine the efficacy of a porous, elastic epicardial patch made from biodegradable polyurethane (poly[ester urethane]urea; PEUU), which was designed to have properties appropriate for the cardiovascular system, using a porcine ischemia–reperfusion MI model.

ETJBS

MATERIALS AND METHODS

Animal Preparation

Twenty-five healthy female crossbred Yorkshire swine, 4 to 5 months old and weighing 23 ± 6 kg, were used in this study. Porcine LV infarcts were created by catheter-based balloon occlusion for 60 minutes and reperfusion of the proximal circumflex artery. Two weeks after MI, patch placement or sham surgery was performed. Before surgery, animals that survived the infarct procedure and had an infarct size meeting the selection criterion, animals with a risk area more than 25% of LV free wall, were randomly assigned to either the PEUU patch placement (MI+PEUU) or sham surgery (MI+sham) group, and were screened by echocardiography to obtain the baseline data. The animal protocol used in the study was approved by the Institutional Animal Care and Use Committee of the University of Pittsburgh (No. 0612885). All animals received humane care in compliance with the ''Guide for the Care and Use of Laboratory Animals'' published by the National Institutes of Health (1996, National Academy Press, Washington, DC). Arterial blood pressure, pulse oximetry, and electrocardiograms were continuously monitored throughout the procedures.

Catheterization for LV Ischemia–Reperfusion Protocol

The animals were anesthetized with ketamine (20 mg/kg) and xylazine (2 mg/kg) administered intramuscularly, followed by intubation and maintenance by mechanical ventilation with oxygen supplemented with 2.0% isoflurane. After placement of the animal in a supine position, the femoral artery was percutaneously cannulated using a 6F arterial sheath with a Seldinger technique under sterile conditions. A bolus of 60 mg/kg heparin and 2 mg/kg of amiodarone was intravenously administered and amiodarone was then continuously infused at 1 mg/min during the procedure to prevent lethal ventricular arrhythmias associated with this model.[16] The ischemia–reperfusion model, which is commonly used in porcine studies of post-MI therapy,[17] was used. The left main coronary artery was selectively engaged using an AL 1 guide catheter (6F; Cordis Corp., Miami, Fla). Using a 3.5 × 12 mm coronary dilatation balloon catheter (Guidant, Santa Clara, Calif), the proximal left circumflex artery was occluded for 60 minutes by balloon inflation (Figure 1).[16] Direct-current cardioversion was performed when sustained ventricular tachycardia or ventricular fibrillation was observed. The animals were then allowed to recover from anesthesia and returned to their housing facility. Buprenorphine (0.05 mg/kg) and cefazolin (30 mg/kg) were administered intramuscularly 2 times per day for 3 days after the procedure. All animals were screened by echocardiography for infarct size as estimated by the percentage of risk area (severe hypokinetic, akinetic, or dyskinetic regions) to the LV free wall area. Animals with a risk area of less than 25% of the LV free wall were excluded from the analysis and humanely killed immediately after echography.

Scaffold Fabrication

PEUU was synthesized according to methods previously described from polycaprolactone (PCL, Mn = 2000, Sigma), diisocyanatobutane (BDI, Sigma), and putrescine.[18] A detailed methodology for scaffold fabrication and characterization is provided in the online data supplement.

Epicardial Patch Placement Surgery

Two weeks after the MI, the animals were sedated with ketamine (20 mg/kg) and xylazine (2 mg/kg) given intramuscularly, intubated, and anesthesia was provided with oxygen with 1.5% inhaled isoflurane. Lidocaine (10 mg/kg) was given to prevent arrhythmias. The heart was exposed through an anterolateral thoracotomy at the fourth intercostal level, and the infarcted cardiac surface was lightly scraped with a surgical knife to introduce blood into the porous PEUU patch and to aid in adhering the entire patch surface onto the surface of the epicardium. The patch was then secured by continuous running suture with 6-0 polypropylene in the PEUU patch group so that the patch covered the infarct area. In the sham surgery group the heart was lightly scraped but no material was implanted. The wound was closed with 4-0 polyglactin absorbable sutures. During the procedure, bupivacaine (0.2 mL/kg) was locally injected into the thoracic wall. The animals were then allowed to recover and returned to their housing facility. Buprenorphine (0.05 mg/kg) and cefazolin (30 mg/kg) were administered intramuscularly 2 times per day for 3 days after surgery for postoperative analgesic treatment and for prophylaxis of surgical site infection, respectively. Echocardiography was performed on each animal at the 4- and 8-week time point after surgery under the anesthesia program described above, but without intubation. All animals were humanely killed at the 8-week time point with potassium chloride bolus dosing (50 mEq/kg) under anesthesia.

Echocardiography

Transthoracic echocardiograms were obtained 2 week after MI as a baseline, 4 weeks after surgery, and at the time of humane killing (8 weeks after surgery) using a Sonos 1500 platform (Hewlett-Packard Company, Palo Alto, Calif) equipped with a 2.5-MHz transducer. Short-axis views of the LV at the level of the papillary muscle were obtained from a right parasternal approach. The end-diastolic (EDA) and end-systolic (ESA) LV internal cavity areas were determined offline by tracing the endocardial border using OsiriX image processing application v.3.7.1. The LV fractional area change (%FAC) was calculated according to the following equation:

$$\%FAC = \frac{EDA - ESA}{EDA} \times 100$$