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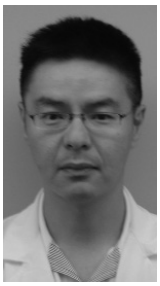
A Novel Technique for Functional Mitral Regurgitation Therapy: Mitral Annular Remodeling



Dr. Kamohara

Keiji Kamohara, MD,[1] Michael Banbury, MD,[2] Anthony Calabro Jr, PhD,[1] Zoran B. Popović, MD,[3] Aniq Darr, BS,[1] Yoshio Ootaki, MD, PhD,[1] Masatoshi Akiyama, MD, PhD,[1] Faruk Cingoz, MD,[1] Chiyo Ootaki, MD,[1] Michael W. Kopcak Jr, BA,[1] Raymond Dessoffy, AA,[1] Jenny Liu, BA,[1] Kiyotaka Fukamachi, MD, PhD[1]

[1]Department of Biomedical Engineering, Lerner Research Institute; Departments of [2]Thoracic and Cardiovascular Surgery and [3]Cardiovascular Medicine, Cleveland Clinic, Cleveland, Ohio, USA

ABSTRACT

Background. Functional mitral regurgitation (MR) plays a pivotal role in the pathophysiology of congestive heart failure, a major cause of cardiac morbidity and mortality. We have developed a mitral annular remodeling procedure through injection of a nonabsorbable substance into the peri-annular tissue of the posterior mitral annulus to reduce the mitral annular dimension in the septal-lateral axis. The purpose of this study is to describe a novel procedure for treatment of functional MR and report its effects on the geometry of the mitral annulus and degree of MR.

Methods. Seven preliminary studies were performed using an epicardial approach in a healthy dog model to establish the feasibility of this injection procedure. Unexpectedly, 2 of 7 healthy dogs had a functional MR of grade 1 to 2+. In these 2 cases, the hemodynamic, angiographic, and echocardiographic assessments were conducted.

Results. A nonabsorbable substance injection was successfully performed on a beating heart without instability of hemodynamics or any evidence of myocardial ischemia in all 7 dogs. In the 2 dogs with a functional MR, it was confirmed that the septal-lateral dimension decreased from 3.2 ± 0.2 to 2.6 ± 0.5 cm and the observed MR was reduced (MR area from 1.2 ± 0.1 to 0 cm^2) without any adverse effects on hemodynamics or coronary circulation (circumflex artery flow, 36.5 ± 0.4 to 40.5 ± 0.1 mL/min).

Conclusion. Off-pump mitral annular remodeling through substance injection may be one procedural option for treatment of functional MR.

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Address correspondence and reprint requests to: Kiyotaka Fukamachi, MD, PhD, Department of Biomedical Engineering/ND20, The Cleveland Clinic, 9500 Euclid Avenue, Cleveland, OH 44195, USA; 1-216-445-9344; fax: 1-216-444-9198 (e-mail: fukamak@ccf.org).

INTRODUCTION

Mitral annular dilatation in the septal-lateral (S-L) axis has been considered one major cause of functional mitral regurgitation (MR) in patients afflicted with congestive heart failure (CHF) [Yiu 2000]. We have been developing a novel procedure: mitral annular remodeling through injection of a nonabsorbable substance into the peri-annular tissue of the posterior mitral annulus. We hypothesize that this procedure will efficiently reduce the S-L dimension by its mass effect, thus improving the degree of functional MR on a beating heart.

To test this hypothesis, a total of 7 preliminary in vivo studies were performed to evaluate the feasibility of the substance injection on a beating heart using a normal dog model. Among the 7 cases, 2 dogs (24.7 ± 0.6 kg) were diagnosed with a functional MR of grade 1 to 2+ prior to the substance injection and provided valuable insights regarding the efficacy of this novel procedure on functional MR. The main focus of this report is to describe the technique used to implement the injection procedure and, in these 2 cases, its effects on the geometry of the mitral annulus and degree of MR.

MATERIAL AND METHODS

This study was approved by the Cleveland Clinic's Institutional Animal Care and Use Committee, and all animals received humane care in compliance with the "Guide for the Care and Use of Laboratory Animals" prepared by the Institute of Laboratory Animal Resources, National Research Council, and published by the National Academy Press, revised 1996.

Substance Description

To date, there have been no reports that describe mitral annular remodeling through substance injection into the cardiac structures in either humans or animal models. Considering the negative effects of commercially available substances in other surgical fields such as plastic and reconstructive surgery and otolaryngology [Russell 1995; Ersek 1997], tyramine-based hyaluronan (TB-HA) hydrogels, which have been under development at the

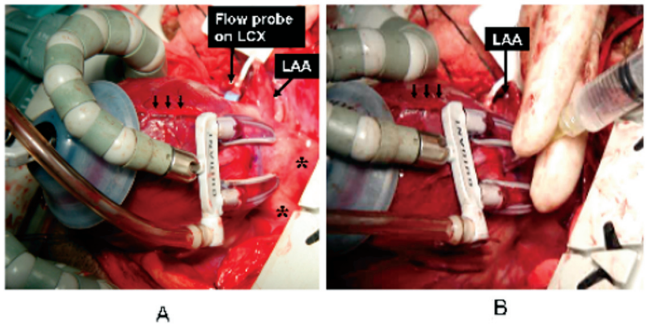

Figure 1. Representative intraoperative views at injection. A, A commercially available cardiac stabilizer was used to stabilize the target region. B, The hydrogel was injected into the peri-annular tissue on a beating heart. The arrows indicate the obtuse marginal artery. LAA indicates left atrial appendage; LCX, left circumflex artery; asterisk (*), left pulmonary vein.

Cleveland Clinic, were chosen as potential injectable substances because of their following characteristics: (1) easy conversion of initial precross-linked injectable form followed by in vivo cross-linking to a single solid implant; (2) resistance to bioresorption; (3) noninflammatory, nonimmunogenic, and nontoxic properties; (4) low evidence of foreign body migration; (5) adjustable physical properties based on concentration of HA; and (6) not particularly malleable nor particularly rigid. This novel hydrogel requires 2 solutions for cross-linking: tyramine-substituted HA containing peroxidase and a dilute hydrogen peroxide solution.

Experimental Procedures

Anesthesia was induced and maintained with intravenous thiopental (20 mg/kg) and isoflurane (0.5%-2.5%), respectively. The animals were placed in the right lateral position with electrocardiogram (ECG) leads attached to the extremities. A fourth left intercostal thoracotomy was performed to access the heart. An 8 F sheath was inserted into the left carotid artery for arterial pressure monitoring, and a 7.5 F Swan-Ganz catheter (Baxter Healthcare, Chicago, IL, USA) was placed into the left jugular vein to obtain hemodynamic data such as pulmonary arterial and central venous pressures. A micromanometer-tipped pressure catheter (SPC 350; Millar Instruments, Houston, TX, USA) was inserted into the left atrium to measure left atrial pressure, and 14.0- and 3.0-mm transonic flow probes (Model A-14 and SB-3.0 mm; Transonic Systems, Ithaca, NY, USA) were each placed around the ascending aorta and the left circumflex artery (LCX) to measure cardiac output and LCX flow, respectively. Hemodynamic data including the LCX flow were collected at baseline. Left coronary angiography was also performed in the 60° left anterior oblique and 30° right anterior oblique planes.

A commercially available cardiac stabilizer (Guidant, Santa Clara, CA, USA) used for off-pump coronary bypass grafting was used to stabilize the target region (Figure 1A). Using 2-dimensional (2D) epicardial echocardiography guidance, the target region and the depth of the injection were determined. First, in the short-axis view, the mid-point of the posterior mitral annulus was determined by compressing the atrioventricular (AV) groove from the epicardial surface with the blunt tip of a surgical tool (Figure 2A). Then, in the long-axis

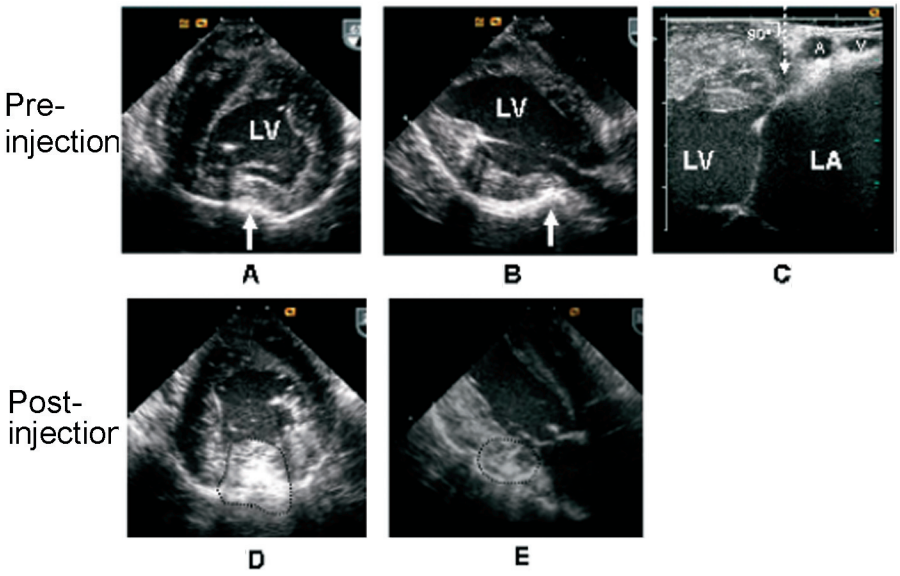

Figure 2. Two-dimensional epicardial echocardiographic images taken during the injection procedure. A and B, The puncture site at the atrioventricular groove was determined by compressing the epicardial surface in the short-axis (solid arrow in A) and long-axis (solid arrow in B) views. C, The depth of the injection site was determined in the view obtained by the linear epicardial probe. The dotted arrow indicates the puncture route that should be at a 90° angle with respect to the epicardial surface. D and E, The hydrogel mass was located in the middle of the posterior mitral annulus in the short-axis view (D). The geometry of the mitral annulus was manipulated in the short-axis (D) and long-axis (E) views. The dotted circles in D and E indicate the hydrogel mass. LV indicates left ventricle; LA, left atrium; A, left circumflex artery; V, coronary sinus.

Hemodynamic and Echocardiographic Data*

	Preinjection	Postinjection
Hemodynamics		
Heart rate, bpm	121 ± 11	118 ± 14
Mean AP, mmHg	79 ± 12	76 ± 13
PAP, mmHg	14.6 ± 1.5	12.7 ± 1.3
LAP, mmHg	8.5 ± 1.6	7.7 ± 1.9
CVP, mmHg	7.7 ± 2.2	6.3 ± 1.0
CO, L/min	3.5 ± 1.3	3.4 ± 0.6
LCX flow, mL/min	36.5 ± 0.4	40.5 ± 0.1
Echocardiography		
MR degree	1-2	0-trace
MR area, cm^2	1.2 ± 0.1	0
S-L dimension, cm	3.2 ± 0.2	2.6 ± 0.5
C-C dimension, cm	3.3 ± 0.5	3.2 ± 0.1

*bpm indicates beats per minutes; AP, arterial pressure; PAP, pulmonary arterial pressure; LAP, left arterial pressure; CVP, central venous pressure; CO, cardiac output; LCX, left circumflex artery; MR, mitral regurgitation; S-L, septal-lateral; C-C, commissure-commissure.

view, the final puncture site at the AV groove was confirmed by delicately adjusting the compression site on the longitudinal line of the left ventricle (LV) that passed on the mid-point determined by the short-axis view (Figure 2B). Finally, the depth of the injection site was determined by measuring the distance from the epicardial surface underneath the LCX and the coronary sinus (CS) to the target region at a 90° angle with respect to the epicardial surface (Figure 2C).

In both Case 1 and Case 2, the determined injection site was approximately 5 mm in depth from the epicardial surface of the AV groove in the middle of the posterior mitral annulus. Using a specially designed needle capable of executing consecutive injections of 2 different solutions without requiring additional puncture sites, 3 and 4 mL of TB-HA hydrogel with subsequent injections of 0.3 and 0.4 mL of hydrogen peroxide were injected into the peri-annular tissue in Case 1 and 2, respectively (Figure 1B). The injection route was at a 90° angle with respect to the epicardial surface in both cases. After the injection, hemodynamic, echocardiographic, and angiographic evaluations were repeated. Following full heparinization, the animal was sacrificed, and the heart was excised for gross examination.

RESULTS

The TB-HA hydrogel injection was successfully performed on a beating heart in both dogs without instability of hemodynamics or any evidence of myocardial ischemia. The Table displays the hemodynamic and echocardiographic parameters at preinjection and postinjection. At baseline, 1 to 2+ of central regurgitant jet (MR area, 1.2 ± 0.1 cm^2) into the left atrium was found without any organic lesions in the mitral apparatus in both cases. After the hydrogel injection, functional MR disappeared (MR area, 0 cm^2) with a decrease in the S-L dimension from 3.2 ± 0.2 cm to 2.6 ± 0.5 cm and no change in the commissure-commissure dimension. No hemodynamic change was observed before or after the hydrogel injection. In addition, no adverse effects on the LCX or CS flows were confirmed in the LCX flow measurements and the angiographic findings including the delayed images.

The 2D echocardiographic images at postinjection revealed that the hydrogel mass was created in the middle of the posterior mitral annulus and that the geometry of the posterior mitral annulus was deformed by the hydrogel mass, resulting in a reduction of the S-L dimension (Figure 2, D and E). Furthermore, a significant decrease in the MR at postinjection was confirmed in the color Doppler image (Figure 3, A and B).

The hydrogel mass was created in the peri-annular tissue of the posterior mitral annulus at the midline between the papillary muscles (Figure 4A), forming a mass size of 19 × 12 mm and 16 × 12 mm in Cases 1 and 2, respectively. As a result, the geometry of the posterior mitral annulus was manipulated, causing a reduction in the S-L dimension without imposing adverse effects on the LCX or CS (Figure 4B).

DISCUSSION

Among the 7 feasibility studies, 2 cases, which were diagnosed with a functional MR of grade 1 to 2+ prior to the substance injection, revealed that the off-pump mitral annular remodeling through the TB-HA hydrogel injection into the peri-annular tissue of the posterior mitral annulus caused a reduction of the S-L dimension of the mitral annulus by its mass effect and consequently reduced the degree of functional MR.

Recently, several new methods of mitral valve repair have been developed. Although Downing et al [2002] and our group [Inoue 2004a, 2004b] have reported new techniques regarding off-pump mitral valve repair procedures, those techniques require general anesthesia and a thoracic incision. On the other hand, Kaye et al [2003] and Liddi-

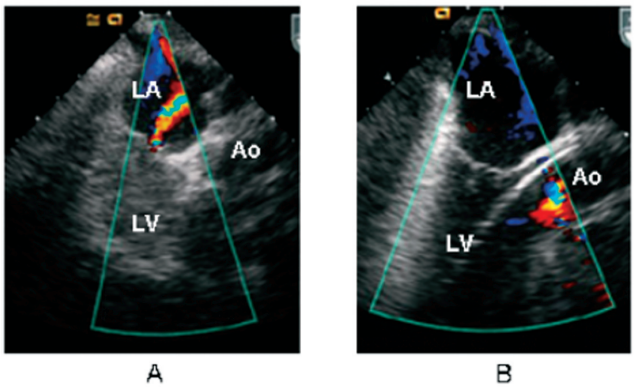

Figure 3. Doppler images taken during the injection procedure. A, Regurgitant Doppler signal into the left atrium (LA) was observed at preinjection. B, No Doppler signal into the LA was found at postinjection. LV indicates left ventricle; Ao, ascending aorta.

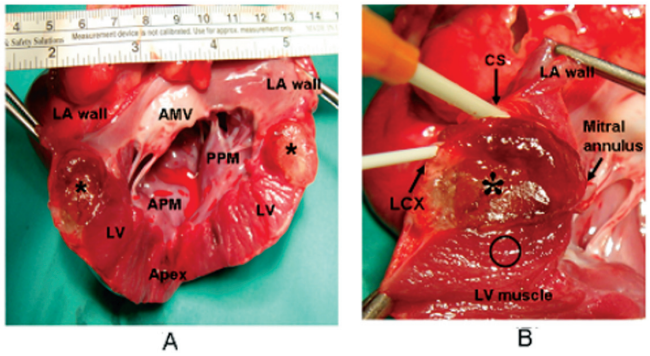

Figure 4. Gross anatomic cross-sectional views of the injection site. A, The hydrogel mass was created in the peri-annular tissue at the mid-point between the papillary muscles. B, The geometry of the posterior mitral annulus was manipulated, resulting in a reduction in the septal-lateral dimension. LA indicates left atrium; AMV, anterior mitral valve; APM, anterior papillary muscle; PPM, posterior papillary muscle; LV, left ventricle; LCX, left circumflex artery; CS, coronary sinus; asterisk (*), hydrogel mass.

coat et al [2003] have reported a new device that can be inserted percutaneously into the CS and great cardiac vein to reduce the mitral annular dimension. However, this technique poses potential adverse effects, such as obstruction or disturbance of the coronary circulation by chronic placement of the device in the CS. In addition, percutaneous edge-to-edge mitral valve repair that does not require device implantation into the CS has been under development. According to 6-month clinical trial results of this technique, however, patients with device failures or subsequent surgery have been reported [Feldman 2005]. To address these mitral valve repair issues, we have been developing a novel procedure: mitral annular remodeling resulting from a nonabsorbable substance injection into the peri-annular tissue of the posterior mitral annulus, without cardiopulmonary bypass or performing a thoracotomy. The peri-annular substance injection can be expected to reduce the S-L dimension of the mitral annulus by its mass effect, improving the degree of functional MR. Considering that the mitral annulus is composed of fibrotic tissue, a direct substance injection into the posterior mitral annulus is even more difficult and cannot make sufficient mass effect due to less compliance of the mitral annulus. Therefore, the peri-annular injection was selected as an injection site in this first animal study.

In 2 of 7 preliminary cases in which the dogs had functional MR, it was confirmed that this mitral annular remodeling procedure produced a reduction of the S-L dimension, thus reducing the degree of MR without any negative effects on hemodynamics, LCX, or CS. Timek et al [2002, 2004] reported that the S-L annular cinching, in particular, at the valve center efficiently reduced acute ischemic MR. The effect of the hydrogel injection at the mid-point of the posterior mitral annulus on the geometry of the mitral annulus and MR is almost similar to that of the central S-L annular cinching. Considering that a >20% (from 22%-30%) reduction of the S-L dimension is required for effective MR treatment [Timek 2002, 2004; Kaye 2003; Liddicoat 2003; Inoue 2004a, 2004b], a larger amount of the TB-HA hydrogel should have been injected because the 3 to 4 mL of hydrogel injections in both cases provided only an approximately 19% reduction of the S-L dimension judging from the echocardiographic data. The disappearance of MR despite a less than theoretically required reduction of the S-L dimension may have been attributed to normal LV function (no mitral annular dilatation or LV remodeling) in both dogs.

In Cases 1 and 2, the TB-HA hydrogel was injected into the peri-annular tissue that consists of fatty and connective tissues at the AV groove. Due to the potential risk of damage to the LCX or CS, a hydrogel injection into the top of the LV muscle (black circle in Figure 4B) would have been a safer alternative. Therefore, in 2 of the 5 remaining feasibility studies, an intramuscular injection was performed. Although the effects of the intramuscular injection on the degree of MR were not evaluated since these dogs did not have MR, it was confirmed that the intramuscular injection was feasible. The intramuscular injection site may be more optimal in decreasing the potential of endocardial perforation by excessive hydrogel injection.

In this series, the feasibility of a hydrogel injection was confirmed. Furthermore, a reduction of the S-L dimension and disappearance of MR were very encouraging, although the data were obtained from only 2 animals. In the next phase of our experiment, a canine tachycardia-induced MR model [Inoue 2004a, 2004b] will be used to accurately assess the effects of mitral annular remodeling following substance injection on the degree of MR and the geometry of the mitral annulus. In this next series, a S-L dimension reduction of greater than 20% will be required. In addition, the route of the hydrogel material injection either into the peri-annular tissue or LV muscle will be thoroughly investigated and an optimal approach determined.

If mitral annular remodeling through substance injection proves to be efficacious in reducing MR, further development of a new percutaneous delivery device capable of injecting the hydrogel substance through the CS will be investigated in the future. This new device will provide patients afflicted with mild to moderate CHF with the option of early restoration of mitral valve competence and prevent the progression of devastating heart failure.

In conclusion, the off-pump mitral annular remodeling by the TB-HA hydrogel injection may be one therapeutic option for functional MR treatment by shortening the S-L dimension, thus remodeling the geometry of the mitral annulus.

ACKNOWLEDGMENT

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