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

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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 cm²) 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.

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...
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...
Hemodynamic and Echocardiographic Data*

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<tr>
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<th>Preinjection</th>
<th>Postinjection</th>
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<tr>
<td><strong>Hemodynamics</strong></td>
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<tr>
<td>Heart rate, bpm</td>
<td>121 ± 11</td>
<td>118 ± 14</td>
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<tr>
<td>Mean AP, mmHg</td>
<td>79 ± 12</td>
<td>76 ± 13</td>
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<tr>
<td>PAP, mmHg</td>
<td>14.6 ± 1.5</td>
<td>12.7 ± 1.3</td>
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<tr>
<td>LAP, mmHg</td>
<td>8.5 ± 1.6</td>
<td>7.7 ± 1.9</td>
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<tr>
<td>CVP, mmHg</td>
<td>7.7 ± 2.2</td>
<td>6.3 ± 1.0</td>
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<tr>
<td>CO, L/min</td>
<td>3.5 ± 1.3</td>
<td>3.4 ± 0.6</td>
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<tr>
<td>LCX flow, mL/min</td>
<td>36.5 ± 0.4</td>
<td>40.5 ± 0.1</td>
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<td><strong>Echocardiography</strong></td>
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<tr>
<td>MR degree</td>
<td>1.2</td>
<td>0</td>
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<tr>
<td>MR area, cm²</td>
<td>1.2 ± 0.1</td>
<td>0</td>
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<tr>
<td>S-L dimension, cm</td>
<td>3.2 ± 0.2</td>
<td>2.6 ± 0.5</td>
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<tr>
<td>C-C dimension, cm</td>
<td>3.3 ± 0.5</td>
<td>3.2 ± 0.1</td>
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*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 cm²) 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 cm²) 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-
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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REFERENCES


