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Mitral Annular Remodeling to Treat Functional Mitral Regurgitation: A Pilot Acute Study in a Canine Model

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ABSTRACT

Background: The aim of this study was to evaluate the feasibility and efficacy of the injection of a nonabsorbable substance into the base of the left ventricle (LV) to treat functional mitral regurgitation (MR).

Methods: Tyramine-based hyaluronan hydrogel was injected into the base of the LV of the beating heart in a canine model of rapid ventricular pacing–induced functional MR (n = 4). The severity of MR was evaluated by epicardial echocardiography before and after hydrogel injection.

Results: The injection improved MR grade from 3.4 ± 0.8 to 1.3 ± 0.5 (P = .006) without inducing hemodynamic instability or any evidence of myocardial ischemia. We noted significant decreases in the septal-lateral dimension at the mitral annulus (3.4 ± 0.4 cm to 2.9 ± 0.3 cm; P = .039) and MR volume (20.6 ± 7.3 mm^3 to 5.2 ± 2.2 mm^3; P = .044).

Conclusions: A novel treatment consisting of hydrogel injection into the base of the LV between the 2 papillary muscles was found to be feasible and effective for reducing functional MR in a canine model.

INTRODUCTION

Recently, several devices have been developed to treat functional mitral regurgitation (MR) [Byrne 2004; Inoue 2004; Maniu 2004; Herrmann 2006] because MR plays a pivotal role in the pathophysiology of congestive heart failure and is a strong prognostic index for cardiac morbidity and mortality. Devising less invasive procedures is a matter of great clinical interest because most patients with functional MR have poor left ventricular (LV) function. Therefore, we have developed a novel treatment, termed *mitral annular remodeling*, by injecting a patented hydrogel [Darr 2009] into LV muscle to restore proper mitral valve (MV) function. This treatment can reduce the septal-lateral (S-L) dimension, improving MR without the use of cardiopulmonary bypass. We previously demonstrated the feasibility of this treatment in healthy dogs [Kamohara 2006]. The purpose of the present study was to evaluate this novel technique in dogs with experimentally induced functional MR.

Drs. Calabro and Fukamachi are inventors of the application of the hydrogel technology described in this manuscript and licensed to Lifecore Biomedical, Inc.

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MATERIALS AND METHODS

Study Design

Functional MR with heart failure was induced in 4 mongrel dogs (mean weight, 26.0 ± 2.9 kg) by rapid ventricular pacing at 230 beats per minute for 4 to 5 weeks [Inoue 2004]. The 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* [ILAR 1996].

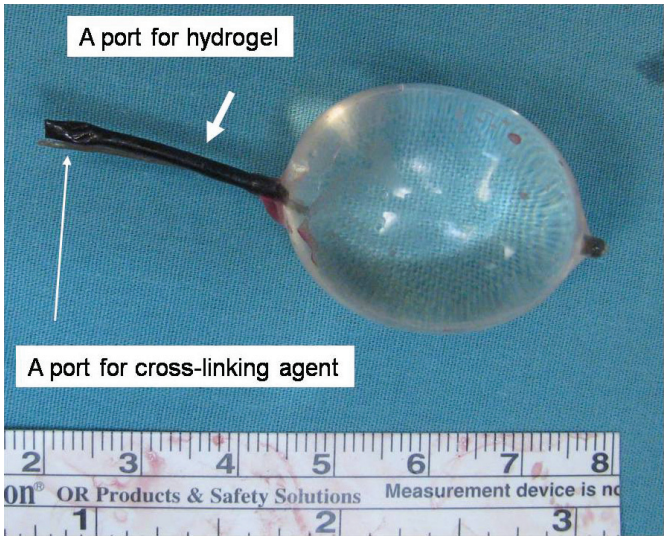

Figure 1. Tyramine-based hyaluronan hydrogel in a balloon with 2 ports. Thick arrow points at a port for the hydrogel; thin arrow indicates a small port for the cross-linking agent.

Table 1. Echocardiography Results*

	Before Injection	After Injection	*P*
MR grade (0 to 4+)	3.4 ± 0.8	1.3 ± 0.5	.006
Mitral annular dimension (S-L dimension) at end-diastole, cm	3.4 ± 0.4	2.9 ± 0.3	.039
LV dimension (S-L dimension) at end-diastole, cm	5.1 ± 0.3	4.6 ± 0.3	.098
MR area (4-chamber view), mm^2	6.5 ± 2.6	1.9 ± 1.0	.022
MR area (2-chamber view), mm^2	7.8 ± 2.7	2.6 ± 1.6	.019
MR volume, mm^3	20.6 ± 7.3	5.21 ± 2.2	.044
EROA, mm^2	0.17 ± 0.05	0.04 ± 0.02	.043
MV tethering area, cm^2	1.46 ± 0.45	0.95 ± 0.19	.175
MV coaptation length, cm	0.34 ± 0.11	0.52 ± 0.04	.044
MR/LA ratio, 4-chamber view	0.33 ± 0.12	0.10 ± 0.05	.024
MR/LA ratio, 2-chamber view	0.44 ± 0.19	0.13 ± 0.07	.027
End-diastolic volume, mm^3	115 ± 20	110 ± 22	.547
End-systolic volume, mm^3	81 ± 19	78 ± 18	.627
Ejection fraction	0.297 ± 0.10	0.293 ± 0.10	.724
MV peak pressure gradient, mm Hg	3.3 ± 2.8	2.5 ± 0.7	.630
MV mean pressure gradient, mm Hg	1.2 ± 0.9	1.0 ± 0.4	.786

*MR indicates mitral regurgitation; S-L dimension, septal-lateral dimension; LV, left ventricular; EROA, effective regurgitant orifice area; MV, mitral valve; MR/LA ratio, ratio of MR jet area to left atrial area.

Nonabsorbable Substance for Injection

A patented tyramine-based hyaluronan (TB-HA) hydrogel was chosen for injection. This TB-HA hydrogel has been under development at the Cleveland Clinic and has been used in plastic and reconstructive surgery and in otolaryngology [Darr 2009].

Auxiliary Instruments

In the previous series, in which the TB-HA hydrogel was injected directly into the LV muscle, a portion of the TB-HA hydrogel leaked into the LV in several cases when >5 mL of the hydrogel was placed [Kamohara 2006]. Therefore, to prevent such leakage, we developed a special biocompatible balloon that could accommodate 10 mL of hydrogel (Figure 1). Several cadaver studies were performed to measure what hydrogel volume was required to decrease the S-L dimension by 20%. These studies proved that at least 10 mL of hydrogel is necessary for this amount of decrease. We also devised an introducer that includes a catheter and a lance with an elbow handle to allow the balloon to be delivered easily. The balloon is made of medical-grade silicone rubber (NuSil Silicone Technology, Carpinteria, CA, USA) and is mounted over a catheter with 2 ports: one for injecting the hydrogel and the other for injecting the cross-linking agent. The gel and cross-linking agent are injected simultaneously into the balloon, where they mix and cross-link.

Preparation for TB-HA Hydrogel Injection

After the pacemaker was turned off to allow resumption of regular sinus rhythm, anesthesia was slowly induced with intravenous ketamine (5 mg/kg) and propofol (1 mg/kg) and maintained with inhalant isoflurane (0.5%-2.5%). A fluid-filled line was placed into the carotid artery to measure arterial pressure. A median sternotomy was performed. A fluid-filled line was inserted into the left atrium (LA) to measure LA pressure, and 14.0-mm and 3.0-mm flow probes (models A-14 and SB-3.0 mm; Transonic Systems, Ithaca, NY, USA) were placed around the ascending aorta and the left circumflex artery (LCX) to measure cardiac output and LCX flow, respectively. Baseline hemodynamic and echocardiographic data were collected before injection. Lidocaine administration (1 mg/kg) was maintained to prevent ventricular arrhythmia.

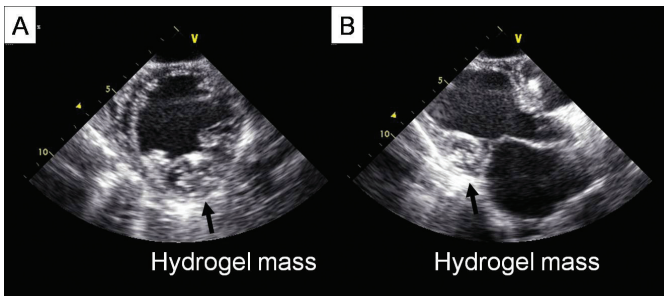

Figure 2. A, Short-axis view of the left ventricle (LV) at the end-systolic phase. Black arrow points at the hydrogel mass in the LV muscle. The hydrogel mass was placed at the midportion between the 2 papillary muscles. B, Long-axis view of the LV at the end-systolic phase. Black arrow indicates the hydrogel mass in the LV muscle. The hydrogel mass pushed the posterior leaflets with basal chordae to the anterior leaflets.

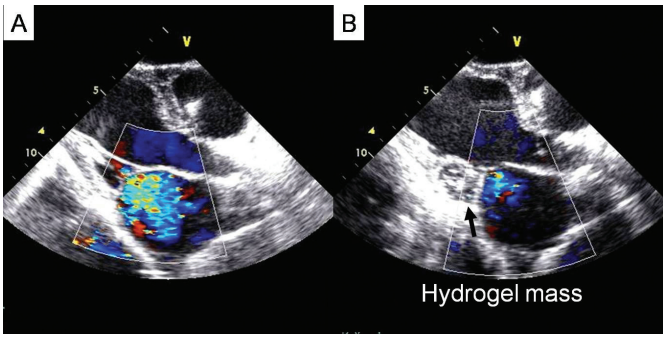

Figure 3. A, Long-axis view of the left ventricle (LV) at the systolic phase. The image shows 3 degrees of mitral regurgitation (MR). B, Long-axis view of the LV at the systolic phase. Black arrow indicates the hydrogel mass in the LV muscle. The hydrogel mass pushed the posterior leaflets and reduced the severity of MR from grade 3 to grade 1.

Material Injection

A cardiac stabilizer (Guidant Corporation, Indianapolis, IN, USA) was used to stabilize the heart. Using 2-dimensional epicardial echocardiography for guidance, we determined the target region to be at the midpoint between the 2 papillary muscles at the level of the mitral annulus. The introducer for the balloon was then inserted into the top of the LV muscle along the LCX, approximately 2 cm away from the target site. A sleeve from the introducer was left in the muscle. A balloon was then placed at the target site through the sleeve. TB-HA hydrogel (9 mL) and hydrogen peroxide (1 mL) were injected simultaneously into the balloon. After completion of the injection, the hemodynamic and echocardiographic evaluations described below were repeated in the same way as before the injection.

Echocardiographic Analysis

Echocardiographic data were collected with a Vivid 7 echocardiography machine (GE Healthcare, Milwaukee, WI, USA). The S-L diameter of the mitral annulus was measured from a 3-chamber apical view, and LV diameters at mid–papillary muscle level were measured via the short-axis view. MR grade was categorized according to the extent and width of the regurgitation jet, and the MR/LA ratio was defined as the ratio of the MR jet area to the LA area. The MR volume and the effective regurgitant orifice area (EROA) were measured by means of the proximal isovelocity surface area method. The MV coaptation length, which was defined as the distance of the leaflet coaptation, and the MV tethering area, which was defined as the area enclosed by the annular plane and 2 leaflets, were measured in apical 4- and 2-chamber views. LV volumes and ejection fraction were determined by the modified Simpson rule with images obtained from the apical 4- and 2-chamber views.

Statistical Analysis

Data are expressed as mean ± SD. The paired Student *t* test was used to analyze data obtained before and after device implantation. A *P* value <.05 was considered statistically significant.

RESULTS

A balloon was used under beating heart conditions to create a TB-HA hydrogel mass. The procedure was successful in all of the dogs without inducing hemodynamic instability or myocardial ischemia. In 1 case, the postinjection echocardiogram revealed that the TB-HA hydrogel mass was located posterior to the midportion between the 2 papillary muscles; thus, MR of grade 2+ remained; however, the degree of MR was smaller than at baseline (3+). Therefore, we used another balloon to place a 5-mL TB-HA hydrogel mass next to the first created mass, which further reduced the severity of the MR to grade 1. In the 3 other cases, a 10-mL hydrogel mass was placed at the base of the LV. Figure 2 shows that the mass was located, as intended, at the midportion between the papillary muscles at the base of the LV. Figure 3 shows an example of the significant reduction in MR observed after the injection. The S-L dimension at the mitral annulus, as well as the MR area and MR/LA area ratio (as assessed via 4- and 2-chamber views), decreased significantly after injection of the hydrogel (Table 1). In addition, the EROA significantly decreased, and the MV coaptation length significantly increased after hydrogel injection. The LV end-diastolic and end-systolic volumes, the ejection fraction, and the MV pressure gradient did not change significantly. The LA pressure decreased after injection, but not significantly (Table 2). These dogs were sacrificed under general anesthesia with a bolus of potassium. At autopsy, the hydrogel with the balloon was in place in the LV wall.

Table 2. Hemodynamic Data*

	Before Injection	After Injection	*P*
Heart rate, bpm	111 ± 9	103 ± 9	.003
Mean arterial blood pressure, mm Hg	69 ± 5	69 ± 10	.918
Left atrial pressure, mm Hg	20.6 ± 2.4	18.0 ± 2.2	.267
Cardiac output, L/min	2.4 ± 0.8	2.1 ± 0.4	.371
Left circumflex artery flow, mL/min	38.5 ± 16.6	31.1 ± 1.2	.662

*bpm indicates beats per minute.

DISCUSSION

The feasibility and efficacy of our novel mitral annular remodeling method of injecting TB-HA hydrogel into the base of the LV muscle was demonstrated in a canine model with functional MR. During the acute-phase study, there was confirmation of LCX flow with no evidence of gross ischemia of the entire myocardium.

Functional MR often occurs in patients with poor LV function, and the optimal treatment for functional MR is still being debated. Although mitral annuloplasty using an annuloplasty ring is the standard surgical technique, several concerns remain in many cases, including the need for cardiopulmonary bypass in such patients and a high rate of MR recurrence due to an inability to reduce the tethering of MV leaflets [McGee 2004; Kuwahara 2006]. Therefore, minimally invasive interventions that use several new devices have been developed [Byrne 2004; Inoue 2004; Maniu 2004; Grossi 2006; Herrmann 2006]. Our concept for using this treatment is simply to restore the effective LV geometry, because an altered geometry is the main cause of functional MR. The advantages of our injection technique include noncontact of the hydrogel with the bloodstream and a lower likelihood for the hydrogel mass to migrate because of its location in the muscle. In addition, our treatment significantly affected the LV geometry and increased the length of coaptation by reducing the S-L dimension without producing any findings of mitral stenosis. MV tethering area was decreased, but not significantly. In addition, this method is so simple that the hydrogel mass possibly could be created by puncturing the LV muscle through the coronary sinus or from the LV cavity and thus delivering it as a percutaneously intravascular therapy.

One limitation of this study is the small number of studied animals (n = 4). Studies of the chronic effects are necessary to evaluate the safety and efficacy of this method over the long term. Successful completion of this procedure in the chronic phase of the study will provide us with preliminary data to support our future program, the development of a new percutaneous device to allow hydrogel injection through the coronary sinus. In the present series, the hydrogel mass was created only at the posterior muscle. It might be feasible to inject this material into other places, such as the base of the papillary muscles, which could reduce the tethering area more significantly [Hung 2008].

In conclusion, a novel mitral annular remodeling method involving the injection of TB-HA hydrogel into the base of the LV muscle was found to be feasible and effective for functional MR in a canine model with stable hemodynamic parameters in acute cases.

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