Transapical mitral valved stent implantation: A survival series in swine

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Objective: To assess short-term survival after transcatheter mitral valve replacement using a unique mitral valved stent design and anchoring system.

Methods: The new nitinol self-expandable valved stent houses a trileaflet glutaraldehyde-preserved bioprosthesis and contains atrial and ventricular fixation systems. Eight pigs underwent transesophageal echocardiogram-guided transapical mitral valved stent implantation through a lower mini-sternotomy. Intracardiac pressure gradients were estimated by transesophageal echocardiogram.

Results: The mean mitral annulus size was 24.6 ± 1.4 mm, and the valved stent size was 26.0 ± 2.6 mm. The average mean transvalvular gradient across the valved stent immediately after deployment, at 6 hours, and after 1 week remained low. The gradient across the neighboring left ventricular outflow tract was not affected. Average animal survival was 7.3 days (8 hours to 29 days). Animals that died before 1 week ($n = 4$) were found at necropsy to have valved stent malpositioning. Animals that survived 1 week or more had accurate deployment and only trace post-deployment paravalvular leak. The causes of death in this latter group were endocarditis ($n = 1$), failure of atrial fixation ($n = 2$), and failure of ventricular fixation ($n = 1$). There was no valved stent embolization in any of the animals.

Conclusion: Adequate function and effective anchoring of the new mitral valved stent allowed for short-term animal survival after transapical mitral valved stent implantation. (*J Thorac Cardiovasc Surg* 2010;140:422-6)

Supplemental material is available online.

Video clip is available online.

Percutaneous mitral valve repair techniques have been developed in an attempt to offer patients less-invasive alternatives to the surgical correction of mitral valve regurgitation. The limitation with current percutaneous mitral valve repair techniques is the lack of true approximation to surgical approaches.¹ Surgery uses more than 1 repair technique to

effectively correct most of the mitral valve pathologies and ensure long-term durability, that is, leaflet repair, chordoplasty, and partial or full ring reduction annuloplasty. Mitral valved stent implantation has the potential to achieve post-procedural results similar to those of surgical repair or replacement. We recently reported successful off-pump transapical mitral valved stent implantation in an acute experimental setting.^{2,3} The current study was designed to assess short-term survival after transcatheter mitral valve replacement using a similar approach.

MATERIALS AND METHODS

Description of the Valved Stent

The new valved stent has 3 components: (1) an atrial fixation system consisting of ultrathin high-density polyester covered metal springs (diameter 35–48 mm); (2) a ventricular body made of a nitinol self-expanding stent frame (Nitinol Devices & Components, Fremont, Calif) that accommodates a bioprosthetic heart valve (diameter, 25–32 mm); and (3) a ventricular fixation system composed of tethering strings (cords) attached to the body of the stent (Figure 1) and designed to be anchored to the ventricular wall. Six glutaraldehyde-preserved aortic valves and 2 trileaflet pericardial valves with expanded diameter ranging from 20 to 31 mm were sutured inside the mitral stents implanted in this experiment. The folded valved stents were 11 to 13 mm wide and 28 to 34 mm long.

Description of the Procedure

Eight Yorkshire pigs, weighing between 41 and 53 kg, underwent transapical off-pump valved stent implantation with a newly designed valved stent. A lower mini-sternotomy was performed under general anesthesia, electrocardiogram, and invasive blood pressure monitoring. The skin was incised 6 to 8 cm over the distal sternum. The xiphoid process was removed,

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Abbreviations and Acronyms

LVOT = left ventricular outflow tract

TEE = transesophageal echocardiography

and the sternum was divided no more than 6 cm in the cranial direction. The pericardium was opened, and a well was created by suturing the cut edges of the pericardium to the skin. Two rows of 3-0 polypropylene pledgeted felt pursestring sutures were placed around the left ventricular apex creating an area exposed for transcatheter access of 3 to 4 cm in diameter. A heparin bolus of 4000 IU was administered intravenously. Transesophageal echocardiography (TEE) was performed, and midesophageal 4-chamber, 2-chamber, and long-axis views were used to measure the maximal diameter of the mitral valve annulus. TEE was subsequently used to position the delivery system and guide the deployment of the new valved stent across the mitral valve. The valved stents were unloaded from a custom front-loading delivery system illustrated previously^{2,3} using a 2-stage procedure. The left ventricular long axis was brought into view by TEE at a 0-degree angle, and the atrial component of the stent was then partially deployed. The position of the delivery system was then adjusted to ensure the atrial fixation springs of the valved stent lie above the mitral valve annulus. A 140-degree angle view was used for the subsequent valved stent positioning. The remaining part of the stent was deployed by retracting the delivery sheath and visualizing the left ventricular long axis with the TEE at a 140-degree angle. Because the Doppler left ventricular outflow tract (LVOT) interrogation cannot be performed from a transgastric position in the swine model, we used the angle correct feature of the Doppler packet to compensate for the axis variation in the mid-esophageal long-axis plane for the estimation of LVOT gradients (Table E1). The delivery sheath was removed, and the anchoring chords were affixed to the myocardium and adjusted to ensure the least paravalvular leak during each experiment. A full TEE examination of the mitral valved stent was performed, including color, pulse-wave, and continuous-wave Doppler assessment of mitral valve inflow and LVOT. A direct contrast left ventriculogram completed the valved stent assessment before the chest closure. A number 10 Jackson Pratt drain (Medex Inc, Dublin, Ohio) was left in the pericardial cavity and attached outside to its portable drainage reservoir. Animals were allowed to recover from anesthesia, had the arterial and venous lines removed, and were subsequently extubated. Animals were then continuously monitored noninvasively for signs of distress for an additional 6 hours, at the end of which they were reintubated and underwent a second TEE examination under general anesthesia. Subsequently, the animals were quickly extubated and allowed to fully recover. They were then given postoperative oral antibiotics for 48 hours and aspirin daily for the duration of the experiment. Animals were assessed several times daily, and those that showed signs of distress were euthanized. A TEE examination under general anesthesia was planned for 1 week after mitral valved stent implantation. Necropsy was performed in all animals. Experiments were carried out, and animals were cared for at the Experimental Surgery Unit at the University of Wisconsin in Madison, a facility accredited by the American Association of Laboratory Animal Care. All animals receive humane care in compliance with the "Principles of Laboratory Animals," formulated by the National Society of Medical Research, and the "Guide for the Care and Use of Laboratory Animals," prepared by the Institute of Laboratory Animal Resources and published by the National Institutes of Health (publication 85-23, revised 1985). The study protocol was approved by the University of Wisconsin Research Animal Resource Center.

RESULTS

No valved stent migration or embolization was seen in any of the animals. Atrial and ventricular ectopic beats

FIGURE 1. A, Ventricular fixation system (ie, tethering cords). B, Prototype valved stent partially loaded onto the deploying catheter.

occurred during preparation of apical access and during valve deployment in all animals. No sustained or hemodynamically relevant arrhythmias were recorded. The mean native mitral valve annular diameter was 24.6 ± 1.4 mm, ranging from 22 to 27 mm (Table 1). The mean mitral valved stent size was 26 ± 2.6 mm, ranging from 23 to 29 mm. All but 3 valved stents were larger than the measured mitral valved annulus (Table 1).

The mitral valved stent was deployed successfully in all animals. There were between 1 and 3 attempts to adequately position and deploy the valved stent across the mitral valve annulus. If maldeployment was recognized at the time of implantation or the amount of mitral regurgitation was more than mild, the valved stent was retrieved, reloaded onto the delivery catheter, and redeployed. The average deployment time was 3.4 ± 1.8 minutes, and the blood loss averaged 268 ± 131 mL. The average mean gradients across the native mitral valve and through the newly deployed mitral valved stent were nearly identical, 2.0 versus 1.8 mm Hg (Table E1). The average gradient through the valved stent increased after 6 hours and at 1 week, but it remained clinically and hemodynamically insignificant (Table E1). No systolic anterior motion of the anterior mitral

TABLE 1. Procedural data

Animal	MV annulus	MV stent	No.	Deployment	Blood loss
	(mm)	(mm)	Attempts	time (min)	
1	22	27	2	3	310
2	25	23	1	3	160
3	27	29	3	2	380
4	25	23	3	5	400
5	25	29	1	1	70
6	25	27	1	7	420
7	24	27	1	3	150
8	24	23	1	3	257
Mean	24.6	26.0	1.6	3.4	268

MV, Mitral valve.

valve leaflet was noted in any of the animals. The average mean gradient across the neighboring LVOT did not change after deployment of the mitral valve stent (Table E1). For a representative color flow TEE examination showing unobstructed LVOT flow and no systolic anterior motion, see the supplementary online video. Left ventriculography was performed through the apical access and before its closure to confirm the TEE findings in all animals. A representative left ventriculogram is provided as a supplementary online video.

Animals survived an average of 7.3 days after mitral valved stent implantation (Table 2). According to the necropsy findings, animals were retrospectively grouped in early and late groups (n = 4 each). Animals that died before 1 week (early group) survived an average of 25 hours (range, 8–42 hours) and were found at necropsy to have valved stent maldeployment at the atrial level (Figure 2). Animals that survived more than 1 week (late group) were alive for an average of 13.5 days (range, 7–29 days). The causes of death were failure of atrial fixation system (ie, fracture of the nitinol springs) in 2 of 4 animals (Figure 3), failure of ventricular fixation system in 1 animal, and pseudomonas bioprosthetic endocarditis in the remaining animal. None of the valved stents had any nitinol stent fractures in the ventricular body of the stent that accommodated the bioprosthesis.

TABLE 2. Outcome data

Animal	Mitral regurgitation			Survived	Failure mechanism
	Post-deployment	6 h	1 wk		
1	Mild	Mild		42 h	Maldeployment
2	Trace	Trace		30 h	Maldeployment
3	Mild	Severe		8 h	Maldeployment
4	Mild	Mild		20 h	Maldeployment
5	Trace	Mild	Mild	29 d	Ventricular fixation
6	Trace	Trace	Moderate	7 d	Endocarditis
7	Trace	Trace	Trace	11 d	Atrial fixation
8	Trace	Trace	Mild	7 d	Atrial fixation
Mean				7.3 d	

DISCUSSION

Transcatheter replacement of atrioventricular heart valves remains the most challenging area of transcatheter valve therapy. Although both aortic and pulmonary valved stent implantations are currently being considered as alternatives to high-risk surgical treatment, transcatheter mitral or tricuspid valve replacement has only been proven as a concept in an acute experimental setting.⁴ Current aortic and pulmonary valved stent designs use the same principles and mechanisms of anchorage of present endovascular stents, that is, stent oversizing and use of radial force. This is because the aortic and pulmonary valved stents are secured mostly in an intravascular position. In fact, the intracardiac portion of these valved stents is responsible for many of the postimplantation complications, such as third-degree heart block requiring pacemaker implantation, which occurs in up to 20% of patients with 1 aortic valved stent,⁵ and stent fractures, seen up to 21% in patients implanted a pulmonary valved stent.⁶ However, the use of radial force for anchoring a mitral valved stent was recently reported with success in a “valve-in-a-valve” model.⁷ This concept of implanting a mitral valved stent inside a surgically placed bioprosthesis has been applied in clinical practice.⁸ Nevertheless, the use of radial force to anchor a valved stent across a “native” atrioventricular valve not only produces an acute distortion of the neighboring structures but also promotes progressive dilation of its dynamic and muscular atrioventricular annulus.^{2,3} Ma and associates⁴ noted a few of these implantation hurdles in their first report of mitral valved stent implantation in an acute series of experiments. They reported successful valve stent functioning in 8 pigs for a period of 30 minutes, after which stent migration and embolization led to demise of all animals within 180 minutes. Inadequate valved stent anchoring results in both paravalvular leakage and stent embolization. Boudjemline and colleagues⁹ reported animal survival up to 1 month after tricuspid valve stent implantation in 4 ewes that did not experienced device embolization. Mitral valved stent implantation carries the highest embolization risk because the valved stent is not only under the stress of cyclical compressions of the muscular part of the annulus but also bears a higher pressure gradient for its valve closure than any other cardiac valve. We thus created a ventricular fixation system represented by valved stent tethering cords to counteract the retrograde displacement force created during valved stent closure and ventricular systole. The axial anchorage created by atrial and ventricular fixation systems allows for unobstructed LVOT flow and reduced compression stress from the cyclic annular contractions. This anchorage system allowed us to use valved stents of different ventricular frame diameters. We learned from our pilot experiments that we do not need to match the diameter of ventricular frame to the size of native mitral valve annulus. Therefore, the valve sizes and their

FIGURE 2. Early failure mechanism: atrial maldeployment. A, Postmortem examination of left atrium showing 1 atrial spring caught underneath the anterior leaflet of the mitral valve. B, Correct deployment.

ventricular frames were chosen at random as long as the difference between the ventricular frame size and the mitral annulus remains less than 10 mm. Three of 8 animals were implanted with valved stents of smaller body diameter than the size of the native mitral annulus (Table 1, animals 2, 4, 8). Because the ventricular frames of the valve stents were only a few millimeters larger than the mitral annulus in 5 of 8 animals and smaller in 3 of 8 animals, no nitinol fractures were seen in the ventricular portion of the stent that carries the bioprosthesis.

Animal survival ranged from 8 hours to 29 days. Three of 8 animals had mild paravalvular regurgitation immediately after deployment. Six hours later, 1 more animal developed mild paravalvular regurgitation and 1 animal with initial mild paravalvular regurgitation developed severe mitral regurgitation. All 4 animals died within 42 hours. Necropsy revealed that these animals had maldeployment of the atrial fixation system at the time of implantation (Table 2, Figure 2). We believe this complication could have been avoided by better integration of TEE and fluoroscopy findings during valved stent deployment.

Half of the animals survived 1 week or more. Necropsy revealed that all but 1 animal, which died of pseudomonas

endocarditis, had structural stent failure, that is, breakage of atrial and ventricular fixations (Table 2, Figure 3). The handmade valved stents created for this study were meant to prove the concept of the new fixation system and not to test its durability. We were content to note the animals could carry out their normal activities for a few weeks after mitral valved stent implantation. Three-dimensional imaging of valved stent positioning along with computational models, such as finite element analysis of the valved stent components, could identify the high stress areas that need to be tailored for enhanced durability. This task is nevertheless complex considering the interactions of the valved stent with the mitral valve environment is complex because of the heterogeneous material composition, dynamic geometric layout, and variable loading conditions.

The transapical approach provided close proximity access to the mitral valve. However, we found that the retrograde access from the higher pressure left ventricular chamber to the lower pressure left atrium was at times difficult. The added complexity of navigating the stent delivery system between intact mitral valve chordae on the beating heart makes the crossing of the mitral valve more challenging than the crossing the aortic valve through a similar transapical approach.

FIGURE 3. Late failure mechanism: failure of the atrial anchoring system. A, In vivo illustration of stent fractures at the highest stress points (arrows). B, Ex vivo illustration of stent fracture (arrow).

Enhanced engineering of the valved stent and delivery system may facilitate implantation of a similar mitral valved stent design through a transseptal antegrade approach.

Study Limitations

One study limitation is that the swine model does not allow direct Doppler interrogation of the LVOT from a transgastric position. The angle-correct feature was used to correct for the off-axis Doppler interrogation of the LVOT from the mid-esophageal position to approximate the LVOT gradients and velocities before and after the implantation.

The study also focused on testing the short-term performance of the new valved stent anchorage system that allowed animal survival after implantation. Durability of this type of valved stent and the long-term effects on myocardial performance of its axial anchorage system are unknown.

CONCLUSIONS

Achievement of secure and reliable anchoring is an essential step for intracardiac valved stent implantation. Short-term animal survival was possible by achievement of effective mitral valved stent function and anchoring. No valved stent embolization was seen in any of the animals in this study or our prior studies. Further refinements in the stent construction and design will be tested to assess its durability.

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TABLE E1. Echocardiographic data (mm Hg)

Animal	Mitral valve gradient (mean)				LVOT gradient (mean)			
	Before deployment	Postdeployment	6 hrs	1 week	Before deployment	Postdeployment	6 hrs	1 week
1	1.0	1.3	3.1		1.3	1.2	1.7	
2	1.4	0.8	1.4		1.2	1.1	1.1	
3	3.5	3.7	2.9		2.4	0.3	0.2	
4	3.0	1.0	1.7		1.7	1	1.7	
5	1.2	2.5	6.6	4.3	1.5	0.8	0.4	2.3
6	1.9	2.8	3.9	5.3	2.7	4.6	1.7	1.3
7	1.1	1.3	4.8	0.9	0.9	0.3	1.7	1.3
8	3.1	1.1	2.4	6.3	2.4	1.4	2.3	2.5
Average	2.0	1.8	3.4	4.2	1.8	1.3	1.4	1.9

LVOT, left ventricular outflow tract.