New Stent for Transapical Mitral Valve Replacement in Acute Swine Experiment

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Research article

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Abstract

Background: Many patients with mitral regurgitation are denied open-heart surgery due to high risk. Transcatheter mitral valve replacement offers an alternative treatment. This study aimed to test the feasibility of a new self-expanding valved stent for transcatheter mitral valve replacement via apex in an acute animal model.

Methods: Eight porcine experiments were performed in the acute study. A left thoracotomy was performed. The new self-expanding transcatheter valved stent was deployed under fluoroscopic guidance within the native mitral annulus via apex. Hemodynamic data, before and after implantation, were recorded. Mitral annulus diameter and valve area were measured using echocardiography. Transvalvular and left ventricular outflow tract pressure gradient were measured invasively.

Results: Seven animals underwent successful transapical mitral valve replacement; the implantation was unsuccessful in one animal. The mean procedure time, defined from placing the purse-string to tightening the purse-string, was 17.14 ± 7.86 min. Hemodynamic data before and after transapical mitral valve replacement showed no difference in statistical analysis. The mean diameter and mean functional area of the self-expanding device after implantation were 2.58 ± 1.04 cm and 2.70 ± 0.26 cm², respectively. Trace to mild central and paravalvular leak was detected in 7 valves. Mean pressure gradient across the self-expanding device was 2.00 ± 0.82 mm Hg; the corresponding gradients across the LVOT were 3.28 ± 1.11 mm Hg. Postmortem examinations confirmed precise device positioning in 7 animals with no signs of LVOT obstruction.

Conclusion: Transcatheter mitral replacement of the new valved stent was confirmed feasible in acute preclinical models. The new stent reveals optimal design parameters.

Introduction

Mitral regurgitation is one of the most common heart valve diseases in the world. Although repair of the valve is the main treatment, replacement is still the gold standard, especially for complex cases or repair failure. However, many patients are denied open-heart surgery due to high risk.

In the past decade, transcatheter aortic valve implantation (TAVI) has developed increasingly and achieved exciting results as a surgical alternative for high-risk patients. Transcatheter mitral valve replacement (TMVR) is in the early clinical stage presently. Several devices and delivery systems have been reported. However, the results have not been encouraging. The technique still faces many challenges because of the complex anatomy of the mitral apparatus, high ventricular pressures, and the relative motion of the mitral annulus.

Learned from our previous experience, we developed a new self-expanding valved stent for transcatheter mitral valve replacement via apex. In this study, we test the feasibility of the new self-expanding valved stent in an acute animal model.

Methods

The new valved stent

The new stent (Fig. 1) is a self-expandable nitinol stent consisting of two components: (1) atrial fixation system with D-shaped design; (2) circular ventricular part accommodating a trileaflet valve made of bovine pericardium. The D-shaped atrial frame can engage with the native mitral annulus. It is conducive to the fixation of the stent and reduces paravalvular leak. The flange of the two edges is relatively wider than the flat aspect and the arc aspect, which specifically fits the saddle-shaped mitral annulus. The asymmetric flange is designed to reduce the impact on the left ventricular outflow tract and prevent stent displacement. The trileaflet bovine valve is mounted on the circular ventricular body. A clip exists on the ventricular portion corresponding to the flat aspect of the D-shaped stent (Fig. 1C). The anterior leaflet can be held between the clip and the ventricular body. A few struts are arranged radially on the ventricular component for anchoring (Fig. 1D arrow). Three tethering strings are attached to the bottom of the stent, which can be fixed to the apex of the heart to prevent stent displacement. The stent frame is covered by a polyester fabric skirt to assist in avoiding paraprosthetic leaks and facilitate tissue ingrowth for long-term fixation and sealing.

Delivery system

The delivery system (Fig. 1D) is designed for transapical access only. The prosthesis is compressed and loaded into a 33Fr delivery capsule. It is advanced into the left ventricle via apex over the wire. Three knobs of the delivery system correspond to the three stages of deployment: atrial body expanding, ventricular expanding, and clip releasing. Rapid ventricular pacing is not required in the whole procedure.

Animal Preparation

The study was approved by the local Ethics Research Board. Animals received care in compliance with the “Guide for the Care and Use of Laboratory Animals” prepared by the Institute of Laboratory Animal Resources and published by the National Institute of Health (NIH publication 85–23, revised 1985).

Eight porcine experiments (mean body weight of the pigs was 46.45 ± 3.72 kg) were performed in this acute study. After administering general anesthesia with tracheal intubation and mechanical ventilation (intramuscular ketamine 22 mg/kg and atropine 0.8 mg/kg, intravenous thiopental 15 mg/kg for induction, and isoflurane 2.5% for maintenance anesthesia), a coronary sinus electrode was inserted into the right internal regular vein under the guidance of Digital subtraction angiography (DSA) for positioning the mitral annulus. The right femoral artery was catheterized for monitoring blood pressure and blood
sampling. The left femoral artery was implanted with a 5F pigtail into the aortic root for locating the aortic valve and angiograph. Arterial pressure, central venous pressure, oxygen saturation, and electrocardiography were monitored continuously.

Transapical procedure

A 5-cm left thoracotomy was performed. Double-purse string sutures were placed at the optimal access site of the left ventricular apex. The size of the valved stent was 10% larger than the diameter of the native mitral annulus measured by CT and epicardial echocardiography. Left ventricular angiography was performed to determine the position of the mitral annulus. A stiff wire was introduced across the mitral valve into the pulmonary vein; the delivery system was advanced along the guide wire into the left atrium, using DSA guidance. The atrial brim was expanded first. At this time, it was necessary to gradually adjust the conveyor to the proper position so that the flat aspect of the D-shaped stent was aligned with the aorta. (There is a directional mark on the conveyor). The delivery system was pulled down until the atrial flange seated firmly on the floor of the left atrium. The ventricular body was deployed without rapid ventricular pacing, and the clip was released to hold the anterior valve. Once the stent position was stable, the stent was completely separated from the conveyor. Three tethering strings attached to the stent were pulled out the apex with the conveyor withdrawn. The apical access site was closed; the strings were fixed at the apex. The procedure was performed under fluoroscopic guidance (Fig. 2).

Device function and hemodynamic impact were assessed with epicardial echocardiography (Fig. 3) and angiography (Fig. 2F) at baseline and 30 min after implantation. The transprosthetic and trans-LVOT pressure gradients were measured. Left ventricular angiography was performed.

Continuous hemodynamic measurements were recorded for another 6–8 hours. The animals were sacrificed for postmortem examination and inspection of the device (Fig. 4).

Statistical Analysis

Data were analyzed with SPSS v19 software for Windows. Variables were reported as mean ± standard deviation (SD), and Student’s T-test was used for comparison.

Results

Seven of eight animals underwent successful transapical mitral valve replacement. In one animal, device positioning failed because of premature stent separation from the delivery system due to incorrect placement, which led the ventricular portion of the stent to migrate into the left atrium. The mean procedure time, defined from placing the purse-string to tightening the purse-string, was 17.14 ± 7.86 min. Hemodynamic data before and after transapical mitral valve replacement appear in Table 1. The mean diameter of the native mitral annulus was 2.46 ± 1.00 cm, and the mean mitral valve area was 4.58 ± 0.29 cm² on echocardiographic evaluation. Comparatively, the mean diameter and mean functional areas of the self-expanding device after implantation were 2.58 ± 1.04 cm and 2.70 ± 0.26 cm², respectively. No statistical difference existed in mitral diameter before and after implantation. However, the functional areas before and after the procedure were significantly different (Sig = 0.00, p < 0.05). Of the 7 successful implants, all valve leaflets had normal mobility and function. Trace or mild central and paravalvular regurgitation was detected in 7 valves (Table 2). The mean pressure gradient across the self-expanding device was 2.00 ± 0.82 mm Hg; the corresponding gradients across the LVOT were 3.28 ± 1.11 mm Hg (Table 1).
Table 1

| No. | Weight (Kg) | HR (bpm) | BP (mm Hg) | CVP (mm Hg) | Valve diameter (mm) | Valve area* (cm²) | Transapical time (min) | Across valve (mm Hg) |
|-----|-------------|----------|------------|-------------|--------------------|-------------------|-----------------------|---------------------|
|     |             |          |            |             | Pr | Po | Pr | Po | Native | stent | Native | Stent |
| 1   | 43          | 125      | 130        | 123/92      | 10 | 9  | 23 | 25 | 4.30   | 2.53  | 33     | 3     |
| 2   | 47          | 126      | 126        | 100/67      | 8  | 7  | 25 | 27 | 4.26   | 2.68  | 20     | 2     |
| 3   | 53.6        | 112      | 110/80     | 106/72      | 9  | 7  | 25.5| 27 | 5.00   | 3.20  | 18     | 2     |
| 4   | 50          | 123      | 112        | 98/53       | 11 | 8  | 25.1| 27 | 4.23   | 2.83  | 11     | 1     |
| 5   | 45.3        | 130      | 112        | 107/70      | N  | 8  | 23.2| 25 | 4.12   | N     | 8.29   | n.a.  |
| 6   | 43.7        | 110      | 113        | 117/73      | 10 | 8  | 23.5| 25 | 4.31   | 2.38  | 10     | 1     |
| 7   | 46          | 126      | 111        | 112/68      | 12 | 10 | 24 | 25 | 4.50   | 2.63  | 13     | 2     |
| 8   | 43          | 112      | 110/81     | 118/73      | 7  | 9  | 23.2| 25 | 4.18   | 2.67  | 15     | 3     |
| Mean| 46.45       | 119      | 120        | 111/72      | 112/69 | 9.38 | 8.29 | 24.06 | 25.75 | 4.36   | 2.70  | 17.14  | 2.00  |
| SD  | 3.72        | 7.54     | 7.84       | 8.55/12.11  | 1.69 | 1.11 | 1.00 | 1.04 | 0.26   | 0.26  | 7.86   | 0.82  |

Across LVOT = Gradient across LVOT; Across valve = gradient across valve; BP = blood pressure; CVP = central venous pressure; HR = heart rate; n.a. = not available (due to failed implantation); post = after implantation; pre = before implantation; SD = standard deviation.

*Differences between native and stent were statistically significant.

Table 2

| No. | CL | PVL         |
|-----|----|-------------|
| 1   | Mild | Mild       |
| 2   | None | Mild      |
| 3   | trace | mild     |
| 4   | Mild | Trace     |
| 5   | None | Moderate to Severe |
| 6   | Mild | Mild      |
| 7   | Trace | mild   |
| 8   | Trace | Mild     |

CL: Central leak, PVL: Perivalvular leak

Postmortem examinations confirmed precise device positioning in 7 animals, with no signs of LVOT obstruction (Fig. 4D). For the failed case, the ventricular body of the stent facing the posterior annulus was deployed at the left atrium. The body facing the anterior annulus was at the true position, and the anterior leaflet was held between the clip and the stent. LVOT was not hindered.

Discussion

Unlike transcatheter aortic valve replacement (TAVR), the development of transcatheter mitral valve replacement is more challenging. The mitral valve is a complicated anatomic apparatus, including mitral leaflets, chordae, and papillary muscles. The non-circular saddle-shaped annulus is pliable and changes during the cardiac cycle. Several vital structures, such as the circumflex coronary artery, atrioventricular node, and left ventricular outflow tract, are adjacent to mitral valve. Specifically, the anterior leaflet of the mitral valve is a part of the left ventricular output tract. All of these create a series of technical difficulties.

Although several challenges exist in TMVR, the TMVR system is rapidly expanding, with over 10 devices currently under development. Several devices, such as Tendyne, Intrepid, Tiara, and CardiAQ, are presently under clinical evaluation. The transapical approach is the chief approach for TMVR. It provides easy access to the mitral valve and a simple stent-release procedure. The use of large-bore catheters (34- to 38-F) is allowed in the transapical approach. The transseptal approach has emerged as a hopeful alternative for TMVR. The technical difficulty and smaller sheath size limit its development.
The atrial portion of our device is "D" shaped, which matches the native mitral annulus. It is conducive to the fixation of the stent and reduces paravalvular leakage. The flange of the two edges is relatively wider than the flat aspect and the arc aspect, which specifically fits the saddle-shaped mitral annulus. The asymmetric flange is designed to reduce the impact on the left ventricular outflow tract and prevent stent displacement. A circular ventricular stent has three anchoring structures. First, radially arranged struts on the ventricular component of the valved stent can penetrate the mitral leaflet and the valvular apparatus and prevent retrograde dislodgement of the device into the atrium during systole. Second, a clip exists on the ventricular portion corresponding to the position of the anterior leaflet of the mitral valve. It is released to hold the anterior leaflet of the mitral valve after the ventricular component opens completely. The design can avoid blocking the left ventricular outflow tract with the native anterior leaflet. It also prevents the device from moving into the left atrium. During the operation, we did not deliberately capture the anterior leaflet. As long as the flat aspect of the D-shaped stent is aligned with the anterior annulus of the mitral valve, the clip can easily hold the anterior leaflet when the left ventricular body is fully opened. Third, three tethering strings are attached to the bottom of the stent, which can be fixed to the apex of the heart to prevent stent displacement. In the early experiments, we found that the posterior side of the stent would shift to the left atrium during the systolic period, which may be related to the insufficient anchoring force between the device and the posterior annulus. We did not add a clip on the posterior of the stent as Tiara, as it involved patent issues. Moreover, we believed that the clip could increase the risk of penetrating the posterior wall of the left ventricle. Therefore, we added three strings attached to the stent symmetrically, which could be pulled out with the delivery system and sutured to the apex. The design achieved good results. No displacement happened in the seven animals.

Our self-expanding stent valve achieved good hemodynamic performance in the acute porcine model. No stent displacement and left ventricular outflow tract obstruction were found. Although a significant difference exists in the effective functional area between the stent valve and the natural valve, it was the same as the conventional bioprosthetic valve. Therefore, this study confirmed the feasibility of the new valved stent and the delivery system. We plan to conduct a long-term animal experiment to observe the reliability of valve stents.

A limitation of this study is using healthy animal models with normal cardiac anatomy and physiology. The healthy pig is significantly different from the patient presenting with functional mitral regurgitation. Another limitation is that the study is an acute experiment. It is necessary to carry out chronic experiments to verify the reliability of valve stents.

Conclusions

The new transapical valved stent is feasible and safe for mitral valve replacement and has good hemodynamic performance in an acute study.

Abbreviations

LVOT: left ventricular outflow tract; TAVI: transcatheter aortic valve implantation; TMVR: transcatheter mitral valve replacement; TAVR: transcatheter aortic valve replacement;

Declarations

Ethics approval and consent to participate: Animal study was approved by the Experimental Animal Ethics Committee of Zhejiang Chinese Medical University. All animals received human care in compliance with the Guide for the Care and Use of Laboratory Animals.

Consent for publication: Not applicable.

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Availability of data and materials: All data generated or analyzed during this study are included in this published article.

Authors’ contributions

(I) Conception and design: LM; (II) Administrative support: LM, YZ; (III) Provision of study materials or patients: YZ; (IV) Collection and assembly of data: YZ, PT; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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