The feasibility evaluation of transapical saddle-shaped valved stent for transcatheter mitral valve implantation

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Abstract

Background: Transcatheter mitral valve implantation (TMVI) is a promising and minimally invasive treatment for high-risk mitral regurgitation (MR). The purpose of this study was to investigate the feasibility of a novel self-expanding valved stent for transcatheter mitral valve implantation via apical access. **Methods:** A novel self-expanding mitral valved stent system was designed and fabricated for the in vivo evaluation. It is consists of an atrial flange and a saddle-shaped ventricular body connected by two opposing anchors and two opposing extensions. During the valve deployment, each anchor is controlled by a recurrent string. TMVI was performed in ten pigs using the valve prosthesis through the apical access to verify technical feasibility. Echocardiography and ventricular angiography were used to assess hemodynamic data and valve function. The surviving pigs were sacrificed four weeks later to confirm stent deployment. **Results:** Ten animals underwent transapical mitral valve implantation with the novel mitral valved stent. Optimal valve deployment and accurate anatomical adjustment were obtained in nine animals. Implantation failed in one case, and the animal died one day later due to stent mismatch. After stent implantation, the hemodynamic parameter of other animals was stable and valve function was normal. The mean pressure across the mitral valve and left ventricular outflow tract (LVOT) were 2.98±0.91mmHg and 3.42±0.66 mmHg, respectively. The macroscopic evaluation confirmed the stable and secure positioning of the stents in the mitral valve. No obvious valve displacement, embolism, and paravalvular leakage were observed four weeks after valve implantation. **Conclusions:** This study proved that the novel mitral valved valve stent is technically feasible in animals. This device features opposing anchors, opposing recurrent strings, and saddle-like ventricular portions, providing structural design details for reducing TMVI complications. However, the long-term feasibility and durability of this valved stent need to be improved and verified.

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Abstract

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Methods: A novel self-expanding mitral valved stent system was designed and fabricated for the in vivo evaluation. It is consists of an atrial flange and a saddle-shaped ventricular body connected by two opposing anchors and two opposing extensions. During the valve deployment, each anchor is controlled by a recurrent string. TMVI was performed in ten pigs using the valve prosthesis through the apical access to verify technical feasibility. Echocardiography and ventricular angiography were used to assess hemodynamic data and valve function. The surviving pigs were sacrificed four weeks later to confirm stent deployment.

Results: Ten animals underwent transapical mitral valve implantation with the novel mitral valved stent. Optimal valve deployment and accurate anatomical adjustment were obtained in nine animals. Implantation failed in one case, and the animal died one day later due to stent mismatch. After stent implantation, the hemodynamic parameter of other animals was stable and valve function was normal. The mean pressure across the mitral valve and left ventricular outflow tract (LVOT) were 2.98±0.91mmHg and 3.42±0.66 mmHg, respectively. The macroscopic evaluation confirmed the stable and secure positioning of the stents in the mitral valve. No obvious valve displacement, embolism, and paravalvular leakage were observed four weeks after valve implantation.

Conclusions: This study proved that the novel mitral valved valve stent is technically feasible in animals. This device features opposing anchors, opposing recurrent strings, and saddle-like ventricular portions, providing structural design details for reducing TMVI complications. However, the long-term feasibility and durability of this valved stent need to be improved and verified.

INTRODUCTION

Mitral regurgitation(MR) is one of the most prevalent valvular diseases in the world. (1) Surgical mitral replacement is the golden treatment for patients with severe MR, but nearly half of patients with severe MR are rejected. (2) Due to lack of surgical treatment, severe MR patients have a high mortality rate. (3) Transcatheter mitral valve implantation (TMVI) is a minimally invasive treatment for severe MR patients with high surgical risk. (4) The clinical effect of the TMVI device is promising. The Tendyne TMVI system has been approved by the European administration for the treatment of MR(5). Several TMVI devices are undergoing preclinical evaluation or clinical trials, including CardiAQ, Twelve, Tiara, and Fortis. (6) Our team designed a novel TMVI valve stent, which is characterized by two opposing anchors points for grasping native leaflets and two recurrent strings points for accurate valve deployment. A coherent delivery system was designed for the tri-step implantation of the TMVI valve stent through transapical access. The feasibility of the technique was verified by in vivo experiments.

MATERIALS AND METHODS

The novel mitral valved stent system

The valved stent is a self-expanding nitinol stent with bovine pericardial tissue leaflets and biocompatible silicone membrane. (Figure1 A-D) The nitinol stent frame was divided into four parts: atrial side, ventricular body, extensions, and anchors. The height of the valved stent is 20mm and the longest diameter of its ventricular body is 27, 30, 33, and 35mm. The ventricular body is like an inverted cone or saddle, attached by two opposing extensions and two opposing anchors. The extension is triangular, opposed with another,

and combined with the ventricular body to reduce the paravalvular leakage. The flange of the atrial side is located at the base of the left atrium and prevents the prosthesis from migrating into the ventricle. The anchor can be abducted by the string while the valve deployment. Two opposing strings stabilize the stent and retrieve it for valve redeployment and readjustment. The structure of the stent is fitted into the complexity of the mitral valve. One anchor is opposite the other and is controlled by a recurrent string, functioning to grasping, engaging, and preserving the native mitral leaflet to avoid valve displacement. The tricuspid pericardial heart valve is mounted on the ventricular body. The nitinol frame is covered with an ultra-thin biocompatible membrane to reduce valve regurgitation.

The valved prosthesis is compressed at the front end of the 28fr delivery system. Each string was loaded inside the delivery system and hung on the anchor in a recurrent direction to control the anchor abduction and stent retrieving. (Figure 1E) Only qualified valve stents are used in animal studies. The releasing and retrieving process of the valved stent system was tested before sterilization.

Animal preparation

The animal study was approved by the local hospital's ethics committee with a project license (NO.2018-DW-006). All animal procedures were completed under the "Guide for the Care and Use of Laboratory Animals" issued by the Ministry of Science and Technology of China. Pigs weighing 55-75Kg were selected for the valve intervention. All animals were fasted and deprived of water eight hours before surgery. Transthoracic cardiac echocardiography was performed to measure mitral anatomy before valved stent deployment. The maximum diameter of the mitral annulus and mitral area were accurately measured for subsequent study. (Figure 2 A&B)

TMVI procedure

Experimental pigs were anesthetized with 4-10mg propofol for induction and maintained with 4-12mg/kg/h propofol. A left anterolateral thoracotomy was performed minimally in the fifth intercostal space for access to the left ventricle (LV) apex. Echocardiography and fluoroscopy were utilized as intraoperative guidance. Heparin (200 IU/kg) was administered intravenously before apical catheterization. An LV apex incision was performed following the echocardiographic measurement and sutured with two box stitches (Polyprolene2-0). A 0.035-inch J-shaped guidewire was inserted into the LV and retrograded across the mitral valve into the left atrium under the guidance of epicardial echocardiography and fluoroscopy. Then it was manipulated into the left inferior pulmonary vein and exchanged with a super-stiff guidewire. After the LV apex incision was dilated, a delivery system with a crimped valve prosthesis and two recurrent strings was introduced into the LV. The prosthesis was rotated to fit the anatomical position (one anchor matched anterior leaflet and another matched and posterior leaflet) and deployed following the tri-step implantation process. If the stent deployment is found to be inappropriate, the mitral stent was retrieved and redeployed. After valve implantation, intraoperative echocardiography was performed to confirm and evaluate the position and function of the implanted valve. (Figure 4) The delivery system was subsequently removed and replaced with a pigtail catheter for fluoroscopy to identify valvular insufficiency, paravalvular leakage (PVL), and left ventricular outflow tract (LVOT) obstruction, and coronary artery obstruction. (Figure 3) Finally, the chest incision was processed routinely. After implantation, all experiment animals received standardized care. All surviving pigs were monitored clinically and then sacrificed for four weeks. All the hearts were explanted for macroscopic evaluation. (Figure 5)

Statistical analysis

The data was recorded, analyzed, and presented as means±SD by SPSS 17.0 software.

RESULTS

Ten pigs received the TMVI procedures using the novel valved stent system. The mean weight of animals was 62.90±5.80Kg, and the mean diastolic diameter of the mitral annulus was 29.30±2.05mm, ranging from 26-33mm. The diameter of the mitral valved stent was 32.00±3.10mm, ranging from 27-35mm. All but one valved stent was larger than the measured mitral annulus. (Table 1)

The mitral stent was deployed successfully in all experiments. The operation time and deployment time were 77.33±11.58 minutes and 27.44±6.99 minutes respectively. The blood loss volume averaged 351.78±41.54 ml. And the transvalvular pressure across the mitral valve and left ventricular outflow tract (LVOT) were 2.98±0.91mmHg versus 3.42±0.66mmHg, respectively. (Table 2)

One animal died after a failed valve implantation and the necropsy found that the novel prosthesis valve immigrated because its size was smaller than the mitral annulus. The hemodynamic parameter was stable in the remaining animals and valve function was normal after stent implantation. The macroscopic evaluation confirmed the stable and secure positioning of the stents in the mitral valve. No obvious valve displacement, embolization, and paravalvular leakage were observed four weeks after valve implantation. However, there were some metallic fractures at the ventricular partial margin of the mitral valve stent in three cases.

DISCUSSION

The surging success of transcatheter aortic valve replacement(TAVI)is speeding up the innovation and transformation in valve disease treatment. (7) The shift from valve replacement with sternotomy to catheter-based valve implantation has been encouraging. (8) The application of TAVI has revolutionized the treatment of symptomatic severe aortic valve stenosis in the past decade. Though most of the patients who received TAVI were elderly, high-risk, and unsuitable for surgical valve replacement, the risk of TAVI was proved to be tolerable and its outcomes are promising. (9) However, transcatheter mitral valve implantation (TMVI) is still at dawn. (10) Though the first-in-man case of TMVI was reported in 2012, the total reported cases in current literature were approximately 300. (11) The Tendyne valve system, the first approved TMVI device, was a great breakthrough. (5) However, many challenges still delay and render the clinical application of TMVI, including the asymmetrical mitral annulus, high-pressure gradients, and lack of secure anatomic structure for valve fixation. Paravalvular leakage or valvular regurgitation should be minimized, and fatal LVOT obstruction should be avoided. (12-14)

We have designed and fabricated a novel catheter-based mitral stent for TMVI that features in saddle-like ventricular portion, two anchors, and two recurrent strings. This main portion of the valved stent valve was saddle-like, which means that the upper sectional (atrial side) area is smaller than the bottom sectional (ventricular side) area. This design was special and conducive to resisting the high-pressure blood by expanding the stress area and then transferring the compression force to the surrounding structure. Besides, the ventricular body is attached by two opposing extensions, thus fitting to the sub-valvular structure, enhancing the valve stability and reducing the paravalvular leakage. The anchoring mechanism was the combination of the atrial flange, two opposing anchors, and suitable radial force. The design of the anchor is significantly important for the TMVI device as the anterior leaflet is a part of the left ventricular output tract. To increase the grasping angle of the anchor, two strings were specifically designed for the anchor abduction. Two strings were previously loaded inside the delivery system in a recurrent direction and hung on paired anchors. During the valve deployment, two strings also keep the stent remaining inside the delivery system and thus make stent retrieving possible. The string can be remained as the artificial chordae tendineae to sustain the stent or be removed easily (because it's placed in a recurrent direction).

In this study, we focus on the technical feasibility of the valve prosthesis. We performed animal experiments to investigate the in-vivo function of the stent and evaluate the possible complications, such as LVOT obstruction, valve regurgitation, paravalvular leakage. Ten animal experiments were undergone TMVI using the valve prosthesis. All valve prosthesis deployments were successful in the animals. In the surviving cases, intraoperative echocardiography and fluoroscopy show the stable hemodynamic function of the Mitral stent without LVOT obstruction or severe paravalvular leakage. These results indicated the technical feasibility of the Mitral stent system in transcatheter mitral valve implantation. According to the TAVI practice, paravalvular leakage was prevalent after valve implantation and remains an unsolved problem. (16) Trace or mild paravalvular leakages were found in all surviving animals, which were caused by high-pressure blood during the diastolic phase. Clinical paravalvular leakage should be followed up in the long-term evaluation.

One pig died one day after valve replacement. Necropsy found that the diameter of the valve prosthesis was

smaller than the maximum diameter of the mitral ring, resulting in stent displacement. These results suggest that the size of the mitral stent should be larger than, but not equal to, the native mitral valve to avoid valve displacement. The mitral valve anatomy, especially the maximum diameter of the mitral annulus, should be accurately evaluated before surgery. In order to make more accurate preoperative imaging evaluation and avoid the possible errors of a single imaging method, a combination of multiple imaging methods should be considered for the anatomic evaluation of the mitral valve. Preoperative imaging results show that the mean diameter of the diastolic mitral ring was 29.33+-2.05mm. The mean diameter of the valved stent used in this study was 32.00+-3.10mm. The diameter of the valve prosthesis exceeds the maximum diameter of the mitral annulus by 10%-15%, which means that the size of the valve prosthesis was larger than the mitral valve orifice.

The mitral valved stent produced in this study for TMVI was designed to validate the feasibility and concept of the new fixation system. In three cases, some nitinol fractures were found along partial ventricular margins of stents. The main causes of metal fatigue are high ventricular pressure and frequent heart contractions. Finite element analysis and durability tests are needed to improve the structural strength of the valved stent in further research.

Limitations

There are several limitations to our animal experiment. This is a feasibility preclinical study on a specifically designed transcatheter mitral prosthesis. Given the pathological change of acute MR are different from chronic MR, we have not performed the TMVI in an acute MR animal model. In this study, the transapical approach provides direct access to the native mitral leaflets. However, retrograde access was at times difficult because of the blood flow interference or sub-valvular structure obstacle. Moreover, this animal experiment was a short-term evaluation for the TMVI prosthesis without the ability to evaluate for long-term mitral device durability. Animal experiments in chronic MR models and subsequent long-term evaluation should be considered in further research.

CONCLUSION

The experiment results demonstrated that the novel transapical mitral valved stent was technically feasible. This device was designed with several structure innovations like strings-controlling-anchor and saddle-like ventricular body to reduce the complications of TMVI, providing a novel potential TMVI device design. However, its durability should be enhanced and the long-term evaluation should be considered in further research.

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Conflicts of interest

The authors declare that there is no conflict of interest.

Author contribution

Yongxin Zhou supervised the research project, designed the Mitral stent system, executed the animal experiment, and modified the manuscript. Kaiqin Wu executed the animal experiment and wrote the manuscript. Shaorui Gu, Ttiancheng Lu, Zhenchuan Liu, Chenglai Dong, Xin Zhang, and Haitao Huang were involved in the animal experiments. Shaorui Gu and Tiancheng Lu also recorded and evaluated the experimental data.

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Figure Legends

Figure 1 Novel mitral valved stent for transcatheter implantation.

(A) Atrial side view of the valve prosthesis. (B) Ventricular side view of the valve prosthesis. (C-D) Lateral side view of the valve prosthesis. The main structure of the valve prosthesis was mainly divided into four parts, including the atrial flange and the ventricular portion, which are attached to two opposing extensions (star marker) and two opposing anchors (rectangular dotted lines). (E) The valve prosthesis is compressed within a delivery system, with recurrent strings (red arrow) hanging from each pair of anchors. Anchor (red triangle) is abducted at an angle by the string for grasping.

Figure 2 Preoperative echocardiography evaluation before the animal experiment

(A) The native mitral valve opening during the left ventricular diastole. (B)The native mitral valve closed during the left ventricular systole without valve regurgitation.

Figure 3 Representative fluoroscopy images after valved stent deployment

(A) The valve prosthesis was successfully deployed in the heart (asterisk labeled prosthesis), and the delivery system was removed and the ventricular angiography was performed with a pigtail catheter (arrow pointing to the pigtail catheter).

(B) Ventricular angiography showed that the valve prosthesis was closed normally in diastole. There is trace paravalvular leakage in this case. No obvious LVOT obstruction was observed. MV=Mitral valve, LV=Left ventricle, LA= Left atrium, Ao= Aorta.

Figure 4 Representative echocardiography images after valve deployment

The valve prosthesis was closed well during the left ventricular systole. (B) Valve prosthesis was opening during the left ventricular diastole. (LV=Left Ventricle, LA= Left Atrium)

Figure 5 Representative images of necropsy

(A)The pig heart atrium was removed to expose the valve prosthesis. The atrial flange of the valved stent is located on the mitral annulus.

(B) The left ventricle tissue was dissected to reveal the valve prosthesis and subvalvular structure. Both anchors successfully clamped the native leaflet (green arrow) and the valve prosthesis was stable in the mitral position. There were no LVOT obstruction, valve displacement, rupture of chordae tendineae or papillary muscle ischemia, or other subvalvular structural injury. The native mitral leaflets are sandwiched between anchors and the ventricular body of the stent.

(C) Careful examination of the valve prosthesis revealed no embolism or nitinol fracture. No leaflets rupture or dislocating was observed.

Tables

Table 1 Procedural data of animal experiments

No.	Weight	Mitral annulus diameter	Mitral valve area	Stent size	Stent area	Operation time	In
	(Kg)	(mm)	(cm2)	(mm)	(cm2)	(min)	(r
1	55	26	676	27	729	92	3
2	64	27	784	27	900	NA	N
3	56	28	729	30	729	75	2
4	59	28	784	30	900	76	2
5	62	30	900	33	1089	65	3
6	69	29	841	33	1089	70	2
7	70	32	1024	35	1225	93	3
8	72	30	900	35	1225	90	2
9	60	33	1089	35	1225	77	2
10	62	30	900	35	1225	58	1

No.	Weight	Mitral annulus diameter	Mitral valve area	Stent size	Stent area	Operation time	In
mean±SD	62.90±5.8	29.30±2.05	862.70±121.24	32.00±3.10	1066.60±193.37	77.33±11.58	2

Note: No.2 Pig died of failed valve implantation after one day and its data was not applicable and excluded.
NA: Not available/applicable.

Table 2 Hemodynamic data during TMVI

No.	Before TMVI	Before TMVI	After TMVI	After TMVI	Transvalvular Pressure	T
	Blood Pressure (mm Hg)	Heart Rate (bpm)	Blood Pressure (mm Hg)	Heart Rate (bpm)	Mitral valve (mm Hg)	L (
1	122/75	57	116/67	48	2	3
2	99/60	61	NA	NA	NA	N
3	118/68	70	126/80	43	4	3
4	130/69	71	117/75	97	3	2
5	133/66	79	128/79	70	2.5	3
6	108/59	80	123/61	71	2.4	2
7	115/75	71	133/85	95	4	3
8	108/64	60	135/86	82	1.6	3
9	113/78	81	123/85	69	3	3
10	135/68	76	119/68	97	4.4	4
mean±SD	118.10±11.26/68.20±6.03	70.6±8.28	126.2±8.41/77.5±9.45	74.7±20.1	2.98±0.91	3

LVOT: Left Ventricular Outflow Tract. NA: Not available/applicable.