


# Feasibility evaluation of the transapical saddle-shaped valved stent for transcatheter mitral valve implantation

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## Abstract

**Background and Aims of Study:** Transcatheter mitral valve implantation (TMVI) is a promising and minimally invasive treatment for high-risk mitral regurgitation. We aimed to investigate the feasibility of a novel self-expanding valved stent for TMVI via apical access.

**Methods:** We designed a novel self-expanding mitral valve stent system consisting of an atrial flange and saddle-shaped ventricular body connected by two opposing anchors and two opposing extensions. During valve deployment, each anchor was controlled by a recurrent string. TMVI was performed in 10 pigs using the valve prosthesis through apical access to verify technical feasibility. Echocardiography and ventricular angiography were used to assess hemodynamic data and valve function. Surviving pigs were killed 4 weeks later to confirm stent deployment.

**Results:** Ten animals underwent TMVI using the novel mitral valve stent. Optimal valve deployment and accurate anatomical adjustments were obtained in nine animals. Implantation failed in one case, and the animal died 1 day later due to stent mismatch. After stent implantation, the hemodynamic parameters of the other animals were stable, and valve function was normal. The mean pressure across the mitral valve and left ventricular outflow tract were  $2.98 \pm 0.91$  mmHg and  $3.42 \pm 0.66$  mmHg, respectively. Macroscopic evaluation confirmed the stable and secure positioning of the stents. No obvious valve displacement, embolism, or paravalvular leakage was observed 4 weeks postvalve implantation.

**Conclusions:** This study demonstrated that the novel mitral valve is technically feasible in animals. However, the long-term feasibility and durability of this valved stent must be improved and verified.

## KEYWORDS

mitral regurgitation, transcatheter mitral valve implantation, valve prosthesis

## 1 | INTRODUCTION

Mitral regurgitation (MR) is one of the most prevalent valvular diseases worldwide.<sup>1</sup> Surgical mitral replacement is the gold standard treatment for patients with severe MR; however, nearly half of the patients with severe MR are rejected.<sup>2</sup> Due to the lack of surgical treatment, patients with severe MR have a high mortality rate.<sup>3</sup> Transcatheter mitral valve implantation (TMVI) is a minimally invasive treatment for patients with severe MR that are at high surgical risk.<sup>4</sup> The clinical effects of TMVI devices are promising. The Tendyne TMVI system was approved by the European Administration for the treatment of MR.<sup>5</sup> In addition, several TMVI devices are undergoing preclinical evaluations or clinical trials, including CardiaQ, Twelve, Tiara, and Fortis.<sup>6</sup>

Our team designed a novel TMVI valve stent, which is characterized by two opposing anchor points for grasping native leaflets and two recurrent string points for accurate valve deployment. A coherent delivery system was designed for tristep implantation of the TMVI valve stent through transapical access. We aimed to verify the feasibility of this technique using *in vivo* experiments.

## 2 | MATERIALS AND METHODS

### 2.1 | The novel mitral valved stent system

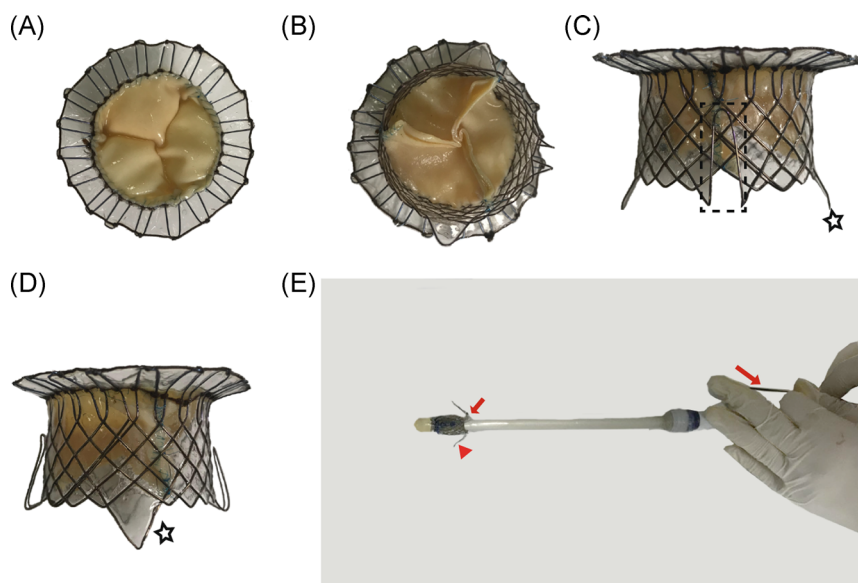
The valved stent was a self-expanding nitinol stent with bovine pericardial tissue leaflets and a biocompatible silicone membrane (Figure 1A–D). The nitinol stent frame was divided into four parts:

atrial side, ventricular body, extensions, and anchors. The height of the valved stent was 20 mm, and the longest diameters of its ventricular body were 27, 30, 33, and 35 mm. The ventricular body resembles an inverted cone or saddle, attached by two opposing extensions and two opposing anchors. The extensions are triangular, opposed to each other, and are combined with the ventricular body to reduce paravalvular leakage (PVL). The flange on 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 during valve deployment. Two opposing strings stabilize the stent and retrieve it for valve redeployment and readjustment. The stent structure was fitted to the complexity of the mitral valve. One anchor is opposite to the other and is controlled by a recurrent string that functions to grasp, engage, and preserve the native mitral leaflet to avoid valve displacement. A tricuspid pericardial heart valve was mounted on the ventricular body. The nitinol frame was covered with an ultrathin biocompatible membrane to reduce the valve regurgitation.

The valved prosthesis was compressed at the front end of the 28 fr delivery system. Each string was loaded inside the delivery system and hung on the anchor in a recurrent direction to control anchor abduction and stent retrieval (Figure 1E). Only qualified valve stents have been used in animal studies to date. The release and retrieval processes of the valved stent system were tested before sterilization.

### 2.2 | Animal preparation

This animal study was approved by the ethics committee of the local hospital with a project license (NO.2018-DW-006). All animal



**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.

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 55–75 kg were selected for the valve intervention. All animals were fasted and deprived of water for 8 h before surgery. Transthoracic cardiac echocardiography was performed to measure mitral anatomy before valve stent deployment. The maximum diameters of the mitral annulus and mitral area were accurately measured in subsequent studies (Figure 2A,B).

### 2.3 | TMVI procedure

The experimental pigs were anesthetized with 4–10 mg propofol for induction and maintained with 4–12 mg/kg/h propofol. Left anterolateral thoracotomy was performed minimally in the fifth intercostal space to access the left ventricle (LV) apex. Echocardiography and fluoroscopy were performed for intraoperative guidance. Heparin (200 IU/kg) was administered intravenously before apical catheterization. An LV apex incision was made following echocardiographic measurement and was sutured with two box stitches (polypropylene 2-0). A 0.035-inch J-shaped guidewire was inserted into the LV and retrograded across the mitral valve into the left atrium under epicardial echocardiography and fluoroscopy guidance. It was then

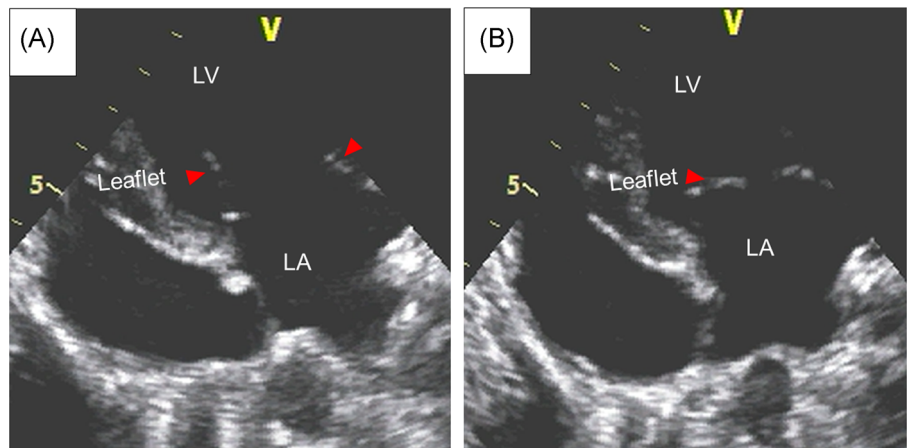
manipulated into the left inferior pulmonary vein and exchanged with a superstiff guidewire. After the LV apex incision was dilated, a delivery system with a crimped valve prosthesis and two recurrent strings was introduced into the LV. The prosthesis was rotated to fit the anatomical position (one anchor matched the anterior leaflet and another matched the posterior leaflet) and was then deployed following the tristep implantation process. If stent deployment was inappropriate, the mitral stent was retrieved and redeployed. Intraoperative echocardiography was performed to confirm and evaluate the position and function of the implanted valve (Figure 3). The delivery system was subsequently removed and replaced with a pigtail catheter to identify valvular insufficiency, PVL, left ventricular outflow tract (LVOT) obstruction, and coronary artery obstruction (Figure 4). Finally, a routine chest incision was performed.

After implantation, all experimental animals received standardized care. All surviving pigs were clinically monitored and killed at 4 weeks. All the hearts were explanted for macroscopic evaluation (Figure 5).

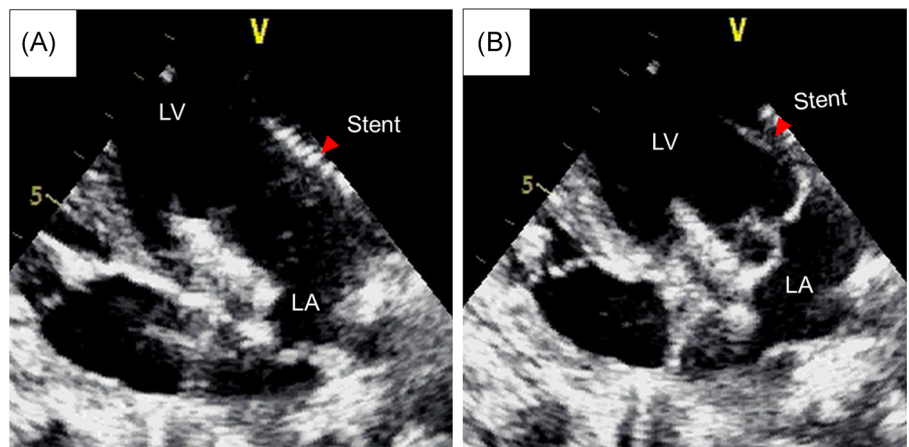
### 2.4 | Statistical analysis

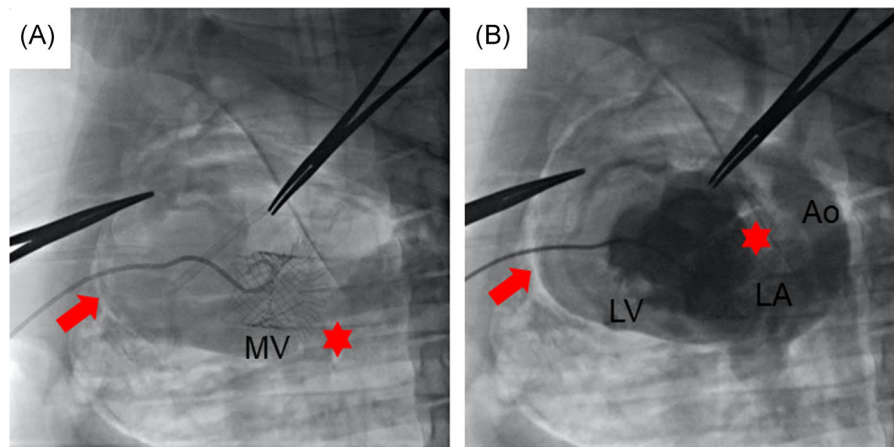
The data were recorded, analyzed, and presented as mean  $\pm$  standard deviation using SPSS 17.0.

**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. LA, left atrium; LV, left ventricle

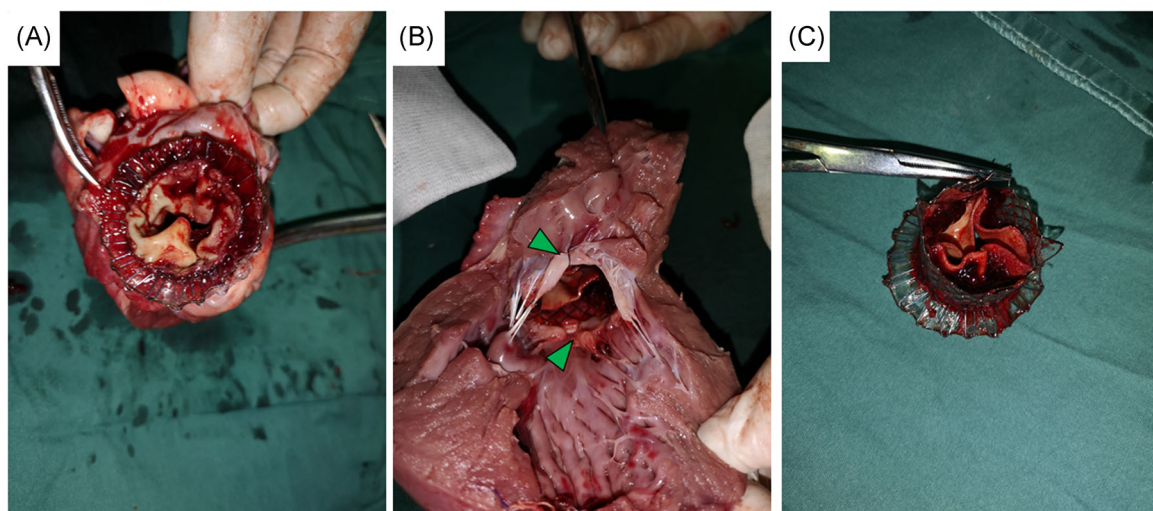


**FIGURE 3** Representative echocardiography images after valve deployment. (A) The valve prosthesis was closed during the left ventricular systole. (B) The valve prosthesis is opened during left ventricular diastole. LA, left atrium; LV, left ventricle





**FIGURE 4** 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. Ao, Aorta; LA, left atrium; LV, left ventricle; LVOT, left ventricular outflow tract; MV, mitral valve



**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 was 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. LVOT, left ventricular outflow tract

### 3 | RESULTS

Ten pigs underwent TMVI using a novel valved stent system. The mean weight of animals was  $62.90 \pm 5.80$  kg, and the mean diastolic diameter of the mitral annulus was  $29.30 \pm 2.05$  mm, ranging from 26 to 33 mm. The diameter of the mitral valve stent was  $32.00 \pm 3.10$  mm, ranging from 27 to 35 mm. All but one valved stent were larger than the measured mitral annulus (Table 1).

The mitral stent was successfully deployed in all experiments. The operation and stent deployment times were  $77.33 \pm 11.58$  min

and  $27.44 \pm 6.99$  min, respectively. The average volume of blood loss was  $351.78 \pm 41.54$  ml. The transvalvular pressure across the mitral valve and LVOT were  $2.98 \pm 0.91$  mmHg and  $3.42 \pm 0.66$  mmHg, respectively (Table 2).

One animal died after failed valve implantation, and necropsy revealed that the novel prosthesis valve immigrated because its size was smaller than that of the mitral annulus. Hemodynamic parameters were stable in the remaining animals, and valve function was normal after stent implantation. Macroscopic evaluation confirmed the stable and secure positioning of the stents in the mitral valve. No

**TABLE 1** Procedural data of animal experiments

No.	Weight (kg)	Mitral annulus diameter (mm)	Mitral valve area (cm <sup>2</sup> )	Stent size (mm)	Stent area (cm <sup>2</sup> )	Operation time (min)	Intervention time (min)	Blood loss volume
1	55	26	676	27	729	92	39	353
2	64	27	784	27	900	NA	NA	NA
3	56	28	729	30	729	75	25	304
4	59	28	784	30	900	76	21	365
5	62	30	900	33	1089	65	35	300
6	69	29	841	33	1089	70	29	433
7	70	32	1024	35	1225	93	31	310
8	72	30	900	35	1225	90	25	394
9	60	33	1089	35	1225	77	28	365
10	62	30	900	35	1225	58	14	342
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	27.44 ± 6.99	351.78 ± 41.54

Note: No. 2 pig died of failed valve implantation after 1 day, and its data were not applicable and excluded.

Abbreviation: NA, not available or applicable.

**TABLE 2** Hemodynamic data during TMVI

No.	Before TMVI		After TMVI		Transvalvular pressure	
	Blood pressure (mmHg)	Heart rate (bpm)	Blood pressure (mmHg)	Heart rate (bpm)	Mitral valve (mmHg)	LVOT (mmHg)
1	122/75	57	116/67	48	2	3
2	99/60	61	NA	NA	NA	NA
3	118/68	70	126/80	43	4	3.3
4	130/69	71	117/75	97	3	2.9
5	133/66	79	128/79	70	2.5	3.2
6	108/59	80	123/61	71	2.4	2.5
7	115/75	71	133/85	95	4	3.9
8	108/64	60	135/86	82	1.6	3.8
9	113/78	81	123/85	69	3	3.3
10	135/68	76	119/68	97	4.4	4.9
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	3.42 ± 0.66

Abbreviations: LVOT, left ventricular outflow tract; NA, not available/applicable; TMVI, transcatheter mitral valve implantation.

obvious valve displacement, embolization, or PVL was observed 4 weeks after the valve implantation. However, there were some metallic fractures at the ventricular partial margin of the mitral valve stent in three cases.

## 4 | DISCUSSION

The surging success of transcatheter aortic valve replacement (transcatheter aortic valve implantation [TAVI]) has accelerated the innovation and transformation of valve disease treatment.<sup>7</sup> The shift

from valve replacement with sternotomy to catheter-based valve implantation has been encouraging.<sup>8</sup> The application of TAVI has revolutionized the treatment of symptomatic severe aortic valve stenosis in the past decade. Although most patients who undergo TAVI are elderly, high-risk, and unsuitable for surgical valve replacement, the risk of TAVI has proven to be tolerable and its outcomes are promising.<sup>9</sup> However, TMVI is still at dawn.<sup>10</sup> Though the first-in-man case of TMVI was reported in 2012, the total number of reported cases in the current literature is approximately 300.<sup>11</sup> The Tendyne valve system, the first approved TMVI device, was a significant breakthrough.<sup>5</sup> However, many challenges still delay and

render the clinical application of TMVI, including the asymmetrical mitral annulus, high-pressure gradients, and lack of a secure anatomic structure for valve fixation. PVL or valvular regurgitation should be minimized and fatal LVOT obstruction should be avoided.<sup>12,13</sup>

We designed and fabricated a novel catheter-based mitral stent for TMVI that features a 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 was smaller than the bottom sectional (ventricular side) area. This design was special and conducive to resist high-pressure blood by expanding the stress area and transferring the compression force to the surrounding structure. In addition, the ventricular body is attached by two opposing extensions, thus fitting the subvalvular structure, enhancing the valve stability, and reducing PVL. The anchoring mechanism was a combination of the atrial flange, two opposing anchors, and a suitable radial force. The design of the anchor is 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 anchor abduction. Two strings were loaded inside the delivery system in a recurrent direction and hung on the paired anchors. During valve deployment, two strings also keep the stent inside the delivery system, thus making stent retrieval possible. The string can remain as artificial chordae tendineae to sustain the stent or can be removed easily (because it is placed in a recurrent direction).

In this study, we focused on the technical feasibility of the valve prostheses. We performed animal experiments to investigate the in vivo function of the stent and evaluate possible complications, such as LVOT obstruction, valve regurgitation, and PVL. Ten animal experiments were performed using valve prostheses. All valve prosthesis deployments were successful in the animals. In the surviving cases, intraoperative echocardiography and fluoroscopy showed stable hemodynamic function of the mitral stent, without LVOT obstruction or severe PVL. These results indicate the technical feasibility of the mitral stent system for TMVI. According to TAVI practice, PVL is prevalent after valve implantation and remains an unsolved problem.<sup>14</sup> Trace or mild PVL was found in all surviving animals, which was caused by high-pressure blood during the diastolic phase. Clinical PVL should be followed up for a long-term evaluation.

One pig died 1 day after the valve replacement. Necropsy revealed 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 prevent valve displacement. Mitral valve anatomy, especially the maximum diameter of the mitral annulus, should be accurately evaluated before surgery. To ensure a 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 anatomic evaluation of the mitral valve. Preoperative imaging results showed that the mean diameter of the diastolic mitral ring was  $29.33 \pm 2.05$  mm. The mean diameter of the valved stent

used in this study was  $32.00 \pm 3.10$  mm. The diameter of the valve prosthesis exceeded the maximum diameter of the mitral annulus by 10%–15%, which means that the size of the valve prosthesis was larger than that of the mitral valve orifice.

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

Our animal experiments have several limitations. This was a feasibility preclinical study of a specifically designed transcatheter mitral prosthesis. Given that the pathological changes in acute MR differ from those in chronic MR, we did not perform TMVI in an acute MR animal model. In this study, the transapical approach provided direct access to the native mitral leaflets. However, retrograde access was difficult because of blood flow interference or a subvalvular structure obstacle. Moreover, this animal experiment was a short-term evaluation of the TMVI prosthesis without the ability to evaluate the long-term mitral device durability. Animal experiments using chronic MR models and subsequent long-term evaluations should be considered in future studies.

## 5 | CONCLUSION

The experimental results demonstrated that the novel transapical mitral valve stent was technically feasible. This device was designed with several structural innovations, such as 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 long-term evaluation should be considered in further research.

## AUTHOR CONTRIBUTIONS

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

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## CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

## ETHICS STATEMENT

This animal study was approved by the ethics committee of the local hospital 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.

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