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Transcatheter mitral valve implantation using a novel system: preclinical results

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Abstract

Background This preclinical study in sheep sought to demonstrate the initial safety and feasibility of a novel transcatheter mitral valve system (Mi-thos valve) composed of a self-expanding frame and a bovine pericardial tissue bioprosthesis. **Methods** The valve was implanted in 26 sheep using a transapical approach for short- and long-term evaluation. The technical feasibility, safety, durability, and valve function were evaluated during and 6 months after the procedure using intracardiac and transthoracic echocardiography, multisliced computed tomography, histological analysis, and electron microscopy. **Results** The success rate of valve implantation was 100%, and the immediate survival rate after surgery was 84%. Five animals died within 90 min after the development of the prosthetic valve due to an acute left ventricular outflow tract obstruction (n = 2) and sudden intraoperative ventricular fibrillation (n = 3). Twelve animals died within 1 month due to acute left heart dysfunction. Mild (n = 5) and moderate (n = 2) paravalvular leakage occurred in seven animals, and two moderate PVL animals died of chronic heart failure within three months. Multimodality imaging studies of the remaining seven animals showed excellent function and alignment of the valves, with no coronary artery obstruction, no left ventricular outflow tract obstruction, no severe transvalvular gradients and no paravalvular leakage. Macroscopic evaluation demonstrated stable, secure positioning of the valve, with full endothelialization of the valve leaflets without injury to the ventricular or atrial walls. Histological and electron microscopic examinations at six months showed no obvious macro- or microcalcification in the leaflets. **Conclusions** Preclinical studies indicate that transcatheter implantation of the Mi-thos valve is technically safe and feasible. The durability, functionality, and lack of leaflet calcification were all verified in animal experiments. The information from these preclinical studies will be applied to patient selection criteria and the first-in-human studies.

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1 Introduction

Mitral regurgitation (MR) is one of the most common valvular heart diseases in the world.[1–3] Although surgery remains the gold standard treatment for MR, approximately one-third of potential candidates for surgical repair or replacement are high risk. Transcatheter mitral valve interventions are valuable alternatives to surgery for those patients.[4,5] Some novel transcatheter mitral valve repair devices have been used in humans with optimal results, such as the MitraClip (Abbott, Abbott Park, IL USA), the NeoChord system (NeoChord, St. Louis Park, MN USA), and the Cardioband system (Edwards Lifesciences, Irvine, CA USA); however, repair techniques are still not possible for all patients with MR and are limited by patient-specific mitral anatomical features.[6] Therefore, transcatheter mitral valve implantation (TMVI) may be an attractive alternative.

In recent years, TMVI has emerged from the laboratory and has been used in humans. Thus far, approximately 300 patients have had implants of all different kinds of TMVI devices.[7,8] The clinical results remain inconsistent, highlighting the need for a device with a better design and the importance of anatomical analysis.[9] We report the initial results of the novel transcatheter mitral valve determined from preclinical studies in sheep.

2 Methods

2.1 Valve and delivery system design

The Mi-thos valve (NewMed Medical Co., Ltd., Shanghai, China) is a self-expanding bioprosthesis with cross-linked bovine pericardial tissue leaflets mounted inside a

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double nitinol self-expanding frame. The inner frame is circular and cylindrical, with three pericardial leaflets and an inner diameter of 29 to 37 mm and a height of 30 mm; it is treated with an anticalcification technique to maintain a consistent, large, and effective orifice area. The atrial portion of the outer frame has a D-shaped design to fit the saddle-shaped mitral annulus; the flange rests on the base of the left atrium, which not only plays a stabilizing role but also allows the endothelialization of the tissue. The ventricular portion of the outer frame is covered with a skirt to minimize paravalvular leakage (PVL) and is secured with barbs to prevent retrograde displacement. The anchoring mechanism of the device relies mainly on the secure barbs in the ventricular portion, which can grasp the native mitral apparatus and oversizing. The ventricular portion is also designed to secure the valve to the fibrous trigones and the posterior shelf of the native annulus of the mitral valve. On the end of the ventricular side, three anchor points permit retrieval of the device for entry into the delivery system (Figure 1A–C). The device is currently available in three sizes in 4-mm increments: 29, 33, and 37 mm. The 41- and 45-mm sizes are under development and will be introduced soon for investigational use. The valve is loaded into a 28–32 Fr caliber transapical delivery system, which is made of polyvinylidene fluoride and polytetrafluoroethylene with a self-dilating tip to facilitate transition through the apex and the mitral valve complex and to reduce system friction. The delivery device consists of a self-dilating tip with a single turn-knob mechanism to allow controlled deployment and is designed to enter the left ventricular apex directly with or without a delivery introducer sheath (Figure 1D).

2.2 Animal study protocols

The animal protocols were approved by the Institutional Animal Care and Use Committee and the Medical Ethics Committee of our local hospital. Twenty-six healthy adult sheep (weight at intervention: 60–70 kg) were used in this study. Catheterization was performed in an animal catheterization laboratory. The operation was carried out under the cooperation of a multidisciplinary team. The animals were anesthetized and intubated endotracheally. All procedures were performed with the animals in the right recumbent position. Intracardiac echocardiography (ICE) using the ACUSON X700 ultrasound system (Siemens Medical Solutions USA, Mountain View, CA, USA) and fluoroscopy were used for intraoperative guidance. The right femoral artery was punctured and cannulated with a 6 Fr sheath. The right femoral vein was also punctured and cannulated with an 11 Fr sheath for insertion of the ICE probe. A coronary sinus electrode was inserted into the coronary sinus through the right jugular vein to help better visualize the mitral annulus and to achieve precise positioning during

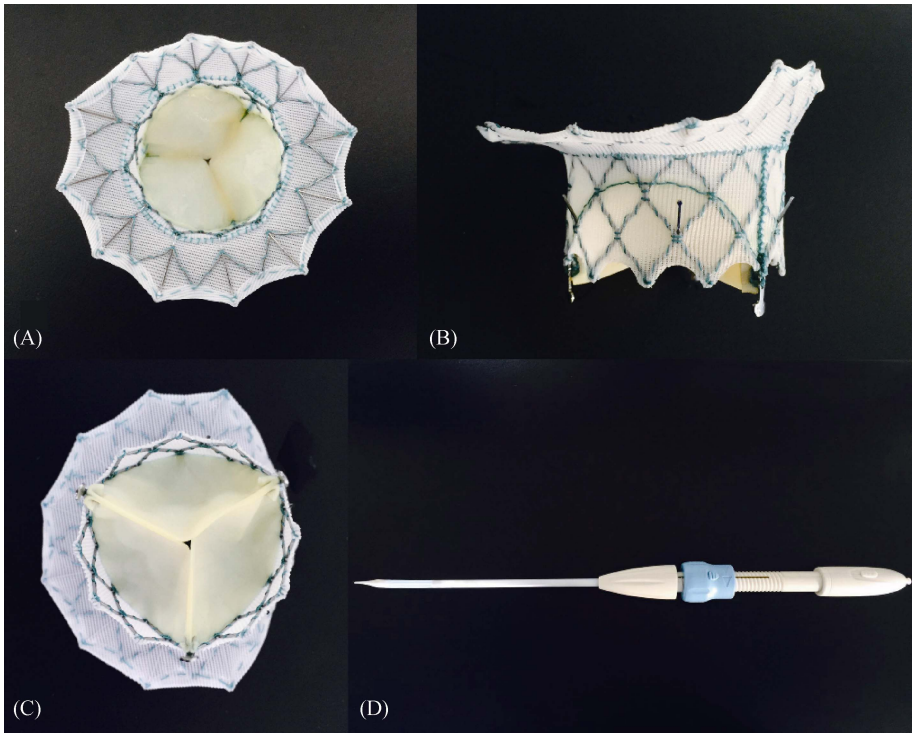

Figure 1. Mi-thos valve and delivery system. (A & C): Sectional view of the D-shaped prosthesis valve; (B): lateral view of the prothesis valve; and (D): delivery system that goes through the apex.

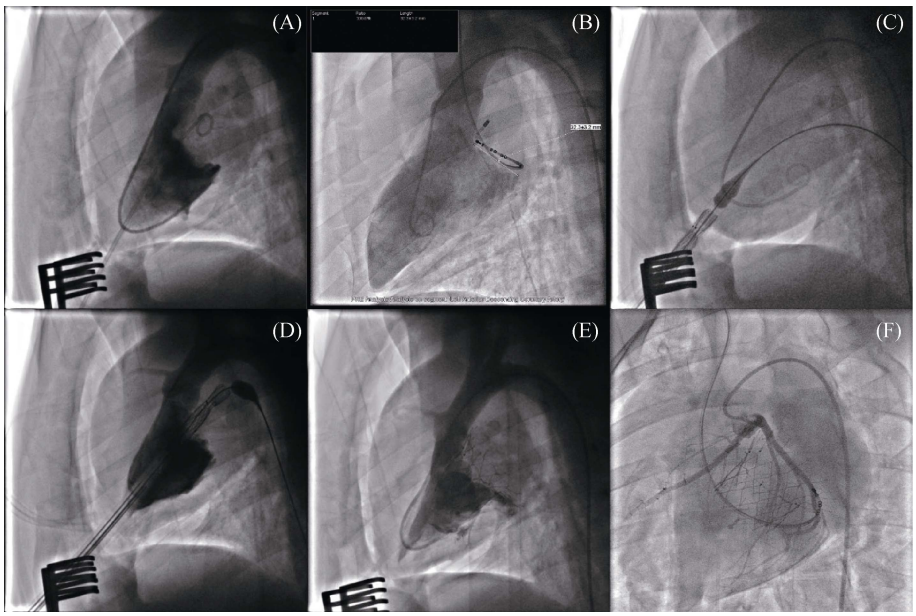

Figure 2. Implantation of the Mi-thos valve in an animal model. (A): Aorta, mitral valve apparatus, and left ventricle were viewed using ventriculography before the procedure; (B): fluoroscopy to show the mitral annulus; (C–E): the Mi-thos valve was inserted via the transapical route and expanded on the mitral annulus; and (F): the position of the valve was evaluated by selective coronary angiography.

the delivery of the bioprosthesis. A 6F pigtail catheter was advanced through the right femoral artery cannula to the ascending aorta and left ventricle. Ventriculograms were taken to show the aorta, the mitral valve apparatus, and the shape of the left ventricle (Figure 2A&B). The precise diameters of the aortic annulus and of the mitral annulus and the length of the left ventricle were measured using preoperative CTA and were double checked by both echocardiography and intraoperative fluoroscopy. A 4-cm subxiphoid minithoracotomy incision was performed, exposing the apex of the left ventricle to allow apical puncture. Two orthogonal U-shaped (purse-string) sutures were placed around the apical entry site. Heparin (100 IU/kg) was administered intravenously. After the apical puncture, a 6 Fr sheath was inserted. A 6F pigtail catheter together with a J-tipped 0.035-inch guidewire was inserted and advanced across the mitral apparatus into the left atrium. Then, the J-tipped 0.035-inch guidewire was manipulated into the distal end of the left inferior pulmonary vein or the left atrium and exchanged with a super stiff guidewire. The valve was loaded into its delivery system, inserted over the guidewire, and advanced retrogradely across the mitral valve into the left atrium (Figure 2C). When we retrieved the outer sheath of the delivery system, the atrial skirt was released while the ventricular portion of the device was still partially confined to the sheath. By rotating the system used to introduce the valve, the D shape of the valve can be adjusted to fit the shape of the native mitral valve apparatus. Radiopaque markers were visualized on the metal frame of the device to achieve accurate alignment and engagement of the flat atrial aspect of the device with the mitral annulus using echocardiographic and fluoroscopic guidance (Figure 2D). The valve was retrievable until the flat atrial segment was released. Then, the whole system was retracted and seated on the atrial side of the mitral annulus. The ventricular portion was deployed and released from the delivery system. Repeat ventriculograms were taken to confirm both the position and the shape of the valve and to determine valvular insufficiency, PVL, left ventricular outflow tract (LVOT) patency, and coronary artery obstruction (Figure 2E & F). After evaluation of valve position and function by ICE (Figure 3), the delivery system was removed.

Following implantation of the valve, all experimental animals received standardized care. Oral aspirin (3 mg/kg) and warfarin (0.1 mg/kg) were administered for 180 consecutive days. At 30 ± 14, 90 ± 14, and 180 ± 14 days after implantation of the device, the animals underwent clinical assessment, tests for complete blood count and blood chemistry analysis, echocardiographic measurements of the degree of mitral regurgitation, the presence of PVL, pressure gradients across the mitral valve and presence of PVL, and multisliced CT to evaluate the positioning and function of the valve and to detect fractures in or deformation of the frame.

In the long-term study, all surviving animals were euthanized at 180 days after implantation and served as the

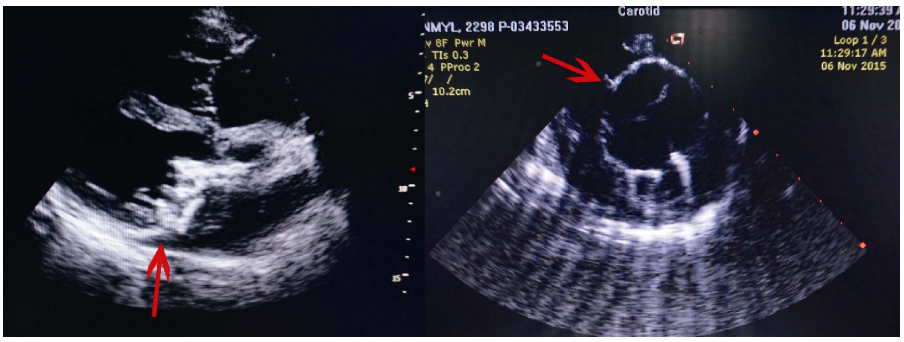

Figure 3. Valve position and function were evaluated from an echocardiogram. The red mark indicates the morphology of the prosthetic valve.

long-term animal model. The hearts were removed for macroscopic evaluation. The surfaces of the Mi-thos valves, the stents, and the polyethylene terephthalate fabrics were examined using pathological sectioning, hematoxylin-eosin and alizarin red staining and scanning electron microscopy.

2.3 Statistical analyses

Data are presented as means ± SD, medians with ranges, or percentages, as appropriate. SPSS 16.0 for Windows (SPSS, Inc., Chicago, IL, USA) was used for the statistical analysis. The *t* test, chi-square test, and Fisher's exact test were used to compare the two groups, where appropriate; $P < 0.05$ was considered statistically significant.

3 Results

3.1 Follow-up and short-term animal models

Mi-thos valves were successfully implanted in all animals. A total of 5 Mi-thos valves of 33 mm and 21 Mi-thos valves of 37 mm were used. The baseline characteristics and procedural data are shown in Table 1. Immediate survival was observed in 21 of 26 (84%) sheep. Five animals died within 90 min due to LVOT obstruction ($n = 2$) and sudden intraoperative ventricular fibrillation that could not be reversed ($n = 3$). Animals suspected of LVOT were autopsied, and macroscopic evaluation showed LVOT obstruction caused by an oversized prosthetic valve or narrowed LVOT. None of the valves migrated or embolized after implantation. The 21 animals that underwent successful valve implantation remained hemodynamically stable throughout the procedure. Postprocedural cardiac catheterization demonstrated patent coronary arteries and no discernible LVOT gradient. Intracardiac echocardiography confirmed good function and alignment of all valves and leaflets, with no LVOT obstruction, no encroachment on the aortic valve, and no transvalvular gradients. Mild PVL was noted in five animals, and moderate PVL was noted in two. None of the surviving animals exhibited hemolysis. Macroscopic evaluation of the explanted hearts in the short-term animal models demonstrated stable, secure positioning of the Mi-thos valve from both the atrial (Figure 4A) and the ventricular (Figure 4B) views.

3.2 Follow-up and long-term animal models

Seven animals died within one week, three died in the second week, and two died in the third and fourth weeks. The cause of death was considered to be acute left heart failure because the animal showed shortness of breath and cough with pink, foamy sputum. Two other animals that were diagnosed with moderate PVL died of chronic heart failure within three months after operation; moderate paravalvular regurgitation and decreased EF value were found by transthoracic ultrasound evaluation. All the animals that died within three months after operation were evaluated by echocardiography before death, and autopsy was performed after death. The five animals with mild PVL survived more than three months. In this experiment, a total of seven animals survived to six months and exhibited normal hemodynamics, and stability was maintained during the follow-up

Table 1. Baseline characteristics and procedural data of the animals that underwent transcatheter mitral valve implantation.

Sex (female/male)	26 (100%)
Weight, kg	75.5 ± 7.2
Diameter of mitral annulus (mm, systolic phase by DSA)	25.8 ± 1.9
Diameter of mitral annulus (mm, diastolic phase by DSA)	30.7 ± 2.6
Diameter of mitral annulus (mm, systolic phase by ICE)	24.8 ± 1.5
Diameter of mitral annulus (mm, diastolic phase by ICE)	31.6 ± 2.1
Size of the Mi-thos valve, mm	36.2 ± 1.6
X-ray exposure time, min	16.9 ± 7.3
Operation time, min	97.7 ± 28.0

Data are presented as mean ± SD unless other indicated. DSA: digital subtraction angiography; ICE: intra-cardiac echocardiography.

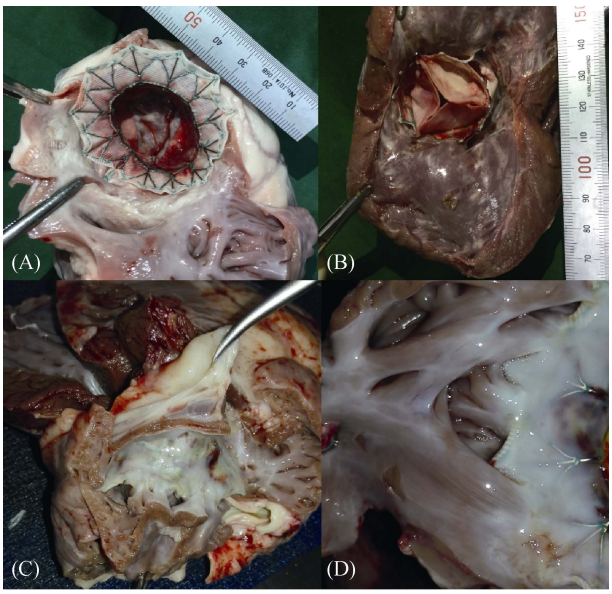

Figure 4. Macroscopic evaluation shows the stable, secure positioning of the Mi-thos valve from both the atrial (A) and ventricular (B) sides. The prosthetic valve was coated with fibrotic connective tissue (C, D).

period. At six months, the remaining seven animals were sacrificed for autopsy. Long-term evaluation of seven sheep showed good valve function and alignment, with no LVOT obstruction, coronary artery obstruction, or transvalvular gradient throughout the 180-day follow-up period. No macroscopic damage, including erosion of the atrial wall or aorta, was noted in the native atria of the individual animals. Cardioscopic examination showed that the valve was well-seated and that the metal struts and Dacron coatings were covered with a white homogeneous fibrotic connective tissue layer along the ventricular struts (Figure 4C). On the atrial side, the prostheses were also coated with fibrotic connective tissue that was adequate for healing and that merged with the atrial tissue (Figure 4D). Gross evaluation revealed that 100% of the atrial element was covered by tissue at 180 days. The leaflets of the explanted Mi-thos valve were soft, flexible, free from thrombus, and intact, without tears or perforations. Histopathological examination using hematoxylin-eosin staining revealed that the collagen fibers of the bioprosthetic valve leaflets of the Mi-thos valve 180 days after implantation were slightly disrupted compared with the unimplanted samples (Figure 5A–D). Alizarin red staining revealed no obvious incrassation and no detectable calcified nodules (Figure 5E–H). Macroscopic analysis of the bioprosthetic valve leaflets using a scanning electron microscope and a transmission electron microscope 180 days after implantation showed that the implanted valve leaflets were coated with the proteins and endothelial cells to form a layer (Figure 6A–D) and that the collagen distribution was regular, without obvious calcified nodules (Figure 6E–L).

3.3 Evaluation using multisliced computed tomography

Multisliced CT images taken following the insertion of the Mi-thos valve showed that the native mitral valves were replaced by the metal skeleton of the Mi-thos frame and that the LVOT and coronary artery were patent (Figure 7A & B). The Mi-thos valve was seated in the desired position without PVL, migration, or fracture of the stent (Figure 7C & D).

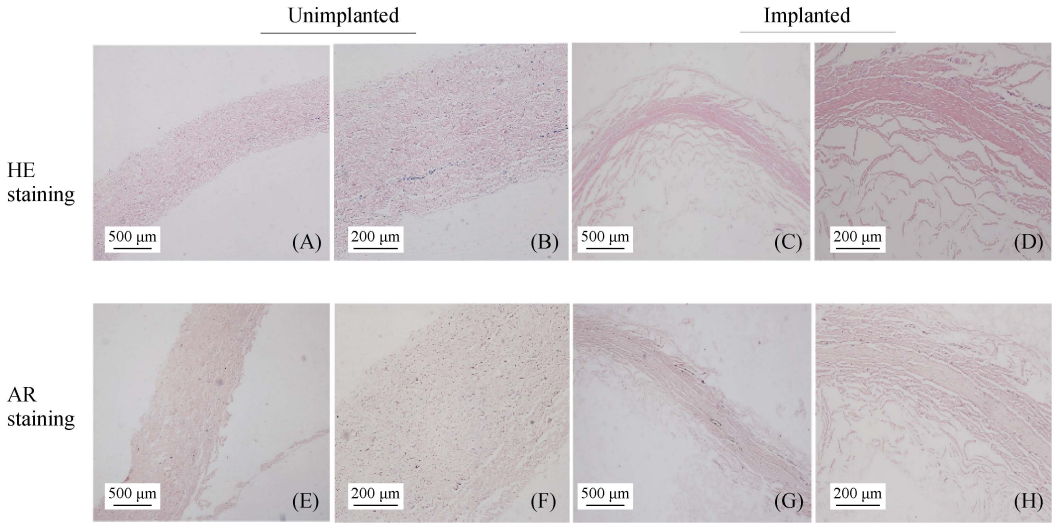

Figure 5. Hematoxylin-eosin staining revealed that the collagen fibers of prosthetic valve leaflets 180 days after implantation were slightly disrupted compared with the nonimplanted samples (A–D). Alizarin red staining revealed no obvious incrassation and no detectable calcified nodules (E–H).

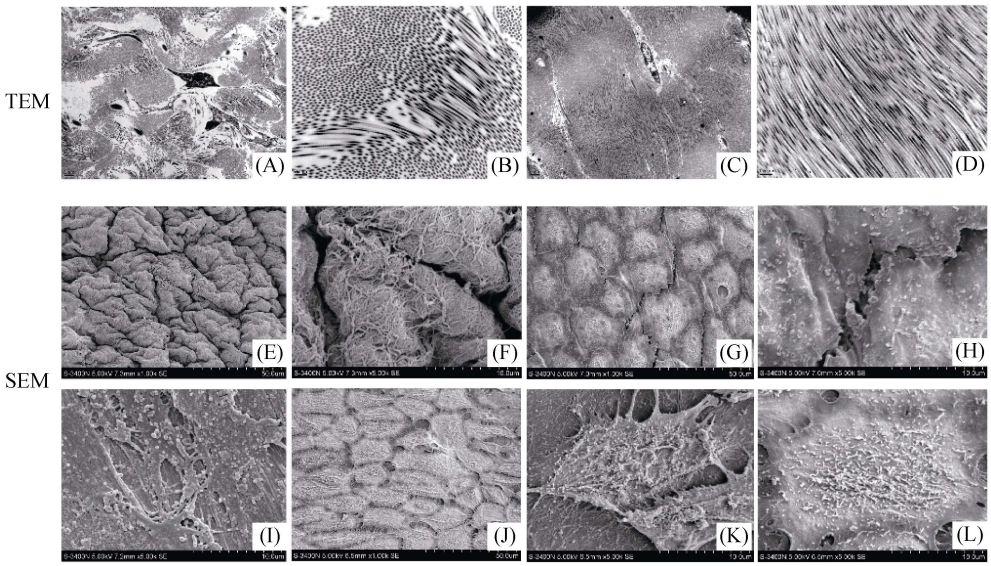

Figure 6. Macroscopic view of prosthetic valve leaflets 180 days after implantation using transmission electron microscopy (A-D) and scanning electronic microscopy (E-L) showing that the leaflets are coated by the proteins and multiple cells and that the collagen distribution is regular, without obvious calcified nodules. TEM: transmission electron microscopy; SEM: scanning electron microscopy.

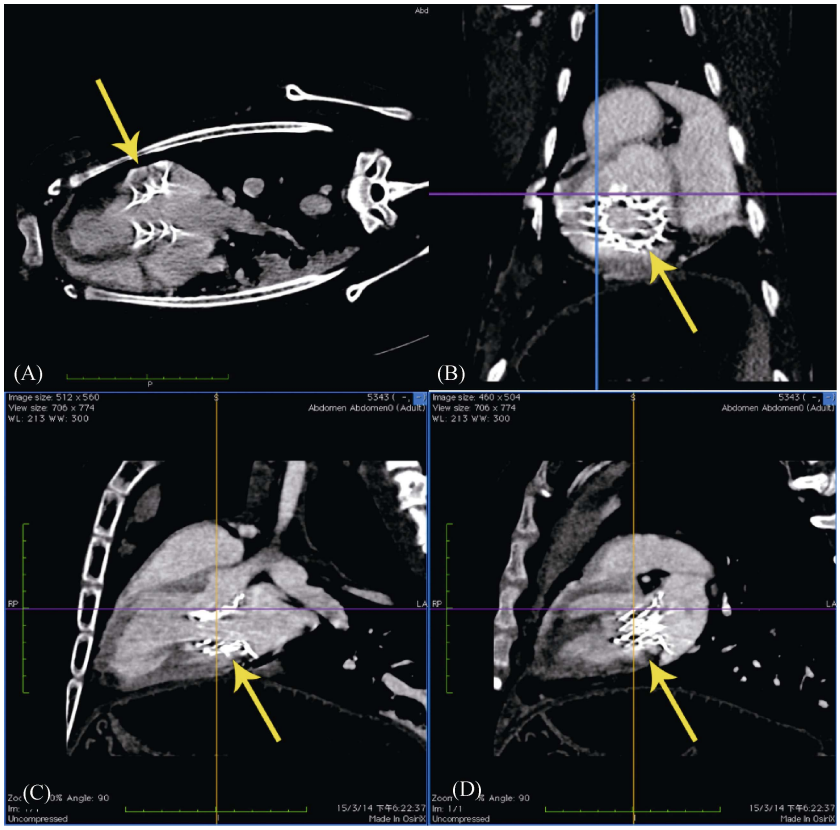

Figure 7. Computed tomographic scan showing the Mi-thos valve seated in the correct position without migration or fracture of the stent in cross-section (A), coronal plane (B) and vertical plane (C & D).

4 Discussion

It has been reported that severe MR affects approximately 2% of the population and that the incidence of severe MR is expected to increase dramatically, with advances in medicine leading to enhanced survival rates.[10] Though open-heart surgery remains the gold standard for treating various mitral valve diseases, cardiopulmonary bypass, cardiac arrest, and

the associated high rates of mortality and morbidity render it inadvisable for elderly and high-risk patients with MR.

Various novel transcatheter valvular technologies have emerged as alternatives to open-heart surgery for high-risk patients, including percutaneous edge-to-edge repair, percutaneous leaflet plication, and direct and indirect annuloplasty.[11–13] However, each transcatheter mitral repair device has its own inherent patient selection criteria and can only be used in a limited number of patients with MR. Due to the complexity of mitral valve diseases, many patients are not candidates for transcatheter repair. Transcatheter mitral valve replacement may provide a viable alternative for inoperable or high-risk patients with MR.[14,15]

Though TMVI reduces MR while preserving the mitral apparatus, many challenges related to the design of the device remain, including accommodating the asymmetrical, multiplanar mitral valve annulus, remaining stable and resistant to displacement or migration, and dealing with the high-pressure gradients that are generated across the mitral valve.[16–18] In addition, valvular regurgitation and PVL after device implantation should be minimized, and the valve must not obstruct the LVOT, occlude the circumflex coronary artery, or compress the coronary sinus.[19–22]

The Mi-thos transcatheter mitral valve was specifically designed to fit the complex anatomical structure of the mitral apparatus. The outside D-shaped frame is designed to fit the native mitral valve annulus and to avoid LVOT obstruction. The barbs on the ventricular side are designed to provide extra fixation beyond the radial expansion force of the device. The inner circular valve stent can ensure optimal valve hemodynamic features and valve durability. Additionally, this device is partially retrievable and repositionable after deployment of the atrial side of the device. The results of the present study showed the safety and feasibility of transapical implantation of the Mi-thos valve. The ovine animal model allowed us to carry out a rapid, straightforward implantation procedure, with an average fluoroscopic time of 16.9 min, a procedure time of 97.7 min, and a procedural success rate of 100%. Instant ICE and follow-up transthoracic echocardiography showed a stable, well-aligned, functional bioprosthesis. We observed that two animals with moderate PVL died of chronic heart failure within three months after surgery, suggesting the importance of preoperative accurate CT evaluation in selecting the right valve type. For five animals with mild PVL, long-term follow-up showed that the PVL was reduced and that no serious complications occurred. Macroscopic evaluation of the explanted hearts showed that the position of the transcatheter valve was stable and secure, with endothelialization of the valve leaflets, the metal frame, and the fabric coatings in the long-term animals. Endodermization of valve leaflets suggests that the preoperative management of artificial valve leaflets is scientific, which is helpful for ensuring the durability of artificial valves, reducing thrombosis and delaying the calcification and decay of valves. The leaflets of the explanted Mi-thos prostheses were mobile and free of clots. There was no evidence of thrombus formation in the heart chambers and no traumatic injuries to the ventricular or the atrial wall near the device. Histological and electron microscopic examinations showed no macro- or microcalcifications up to 180 days after implantation.

According to our limited experience, selection of an appropriately sized prosthesis is the first step toward successful implantation of a transapical mitral valve.[23] Unlike the aortic annulus, the mitral annulus is more dynamic and harder to measure.[24] There is also a large difference in the respective measurements of the mitral annulus taken during the systolic and diastolic phases.[25] We routinely measure the mitral annulus during the diastolic phase with echocardiography and CT angiography (CTA). Sometimes, there is also a large difference between the measurements obtained using these two imaging tools. We prefer to select the size of the device based on the average of the measurements obtained from CTA images. Usually, we select a Mi-thos prosthesis that is 3 to 5 mm larger than the native mitral annulus to prevent possible migration of the device and PVL. Other important considerations in achieving a successful transapical mitral valve implant include alignment and stable anchoring. Precise positioning is crucial, and one should be sure to verify and adjust the orientation of the device after it is partially released. Finally, LVOT obstruction is the most frequent and fatal complication after TMVI. To prevent LVOT obstruction, one must avoid selecting a device that is too large. Therefore, CTA perioperative evaluation is of paramount importance.

4.1 Limitations

Our preclinical study has several limitations. First and foremost, the ovine model is a physiological model and does not allow us to mimic pathological MR. Though we selected sheep of weights similar to those of patients, the heart function of the animals was normal, whereas that of possible candidate patients would be poor. Additionally, the size of the mitral annulus of a possible candidate patient would be much larger than those of the sheep used in this study. Furthermore, the current device is 28–32 Fr, which can only be implanted via a transapical approach, which might limit the use of the technique. Finally because the Mi-thos is a self-expanding valve, it is unknown how the system would behave in a partially or severely calcified

mitral apparatus. Careful selection of clinical cases for the initial human clinical trials should be conducted before the first-in-human applications.

4.2 Conclusions

Using an ovine model, we demonstrated that implantation of the Mi-thos valve is feasible and relatively straightforward and results in a stable, well-functioning mitral valve bioprosthesis. The data and information will be used to further refine the method before beginning a clinical study.

Acknowledgements

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