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Original article

# Balloon-expanding stent and delivery system for transcatheter aortic valve implantation: An animal study

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## Abstract

**Objective:** To evaluate the feasibility and satefy of transcatheter aortic valve implantation in animals by using a new balloon-expanding valved stent.

**Methods:** The balloon-expandable stent is made from cobalt-based alloy material and designed with a tubular, slotted structure. Fresh bovine pericardium was treated, sutured and fixed on the balloon-expandable stent. Ten healthy sheep (five males and five females), weighing an average of (25.16 ± 1.83) kg, were selected to undergo transcatheter implantation of the valve stents. The function of the valve stent was evaluated by angiography, echocardiography, and histology six months after the procedure.

**Results:** Of the ten experimental sheep, two sheep died during the operation because the higher position of the artificial valve affected the opening of the coronary artery. We successfully implanted the aortic valve stent in other eight sheep; however, one sheep died of heart failure two weeks after the operation due to the lower position of the valve stent. The valve stents were implanted in the desired position in seven sheep. Ascending aortic angiographic and autoptic findings immediately after the operation confirmed the satisfactory location and function of the valved stent. Echocardiography, angiography, and histology at six post-operative months confirmed the satisfactory location and function of the valve stent.

**Conclusion:** We successfully implanted our new valve stent as a replacement of native aortic valve via the transcatheter route with satisfactory outcome.



*Keywords:* Percutaneous; Aortic valve replacement; Balloon-expandable stent; Stent shifting

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## Introduction

Degenerative calcific aortic stenosis has become one of the most common adult valvular diseases.[1] Surgical aortic valve replacement is an effective treatment for severe aortic stenosis. However, many patients with severe aortic valve stenosis do not undergo surgery because of advanced age and life-threatening comorbidities. Since transcatheter aortic valve implantation (TAVI) was first accomplished in 2002, TAVI has been successfully used in clinics[2] and has developed rapidly. It is gradually becoming a substitution therapy for severe aortic stenosis in patients with high risk of surgery.[3] We developed a new balloon-expandable valve stent and delivery system. In the present study, we evaluated the feasibility and safety of transcatheter implantation of a new balloon-expandable valve stent into the aortic valve position of sheep.

## Methods

### *Construction of a balloon-expandable valve stent*

The valve stent and delivery device (Fig. 1) were produced by LePu Medical Technology (BeiJing Co., Ltd, China), according to our design and instructions. The balloon-expandable stent is made from cobalt-based alloy material and designed with a tubular, slotted structure. The stent was 24 mm in height, with diameter sizes of 20, 23, and 26 mm.

The prosthetic heart valve is made from bovine pericardium. Fresh bovine pericardium was washed repeatedly, after removing the adipose tissue on its surface, and it is rinsed in cold saline solution until no blood color was found. The bovine pericardial tissue material was treated with Hank's buffer for 8–12 h and 0.6% glutaraldehyde solution for 36 h at 4°C for sterilization. After washing repeatedly with saline solution, the tissue material was agitated by vibration in a formic acid dilution solution for 1 h. Then, the valve was placed in a mixture of 2-(*N*-morpholino)-acetic acid buffer solution (20 g/L), 1-ethyl-3-(3-dimethyl aminopropyl)-carbodimide (5.8 g/L), *N*-hydroxy-succinimide (0.7 g/L), and hexanediamine (7.2 g/L) at pH 5.5 for 18–24 h and stored in a glutaraldehyde solution in the refrigerator.

The treated bovine pericardium was cut into three leaflets, with the two ends of each leaflet overlapping. One end of a leaflet was opposite that of another leaflet. The two ends of each leaflet were sutured with a 7–0 polypropylene suture material and then fixed inside the stent, forming three leaflets. A polyester cloth was used to cover the one-third portion of the valve stent to reduce perivalvular leakage (Fig. 1A and B). The valve stent was stored in 0.3% glutaraldehyde solution. Before application, 75% alcohol was used for disinfection and sterilization and normal saline solution was used for rinsing.

### *Stent delivery system*

The stent delivery system is comprised of a hemostatic loader sheath, a 20F artery sheath, an inner dilator, and a delivery catheter (Fig. 1C). The delivery catheter was made of polytetrafluoroethene with a superlubricious hydrophilic coating. The design of the deflectable forepart of the delivery catheter was made to facilitate passage of the valve stent through the curve of aortic arch. The function of the deflection is accomplished by rotation of the handle of the delivery catheter. The proximal portion of a delivery catheter is

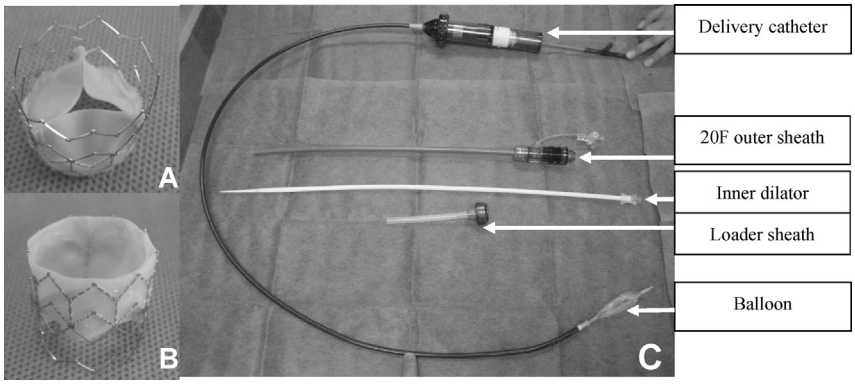


Fig. 1. Valve stent and delivery system; A. Upper view of valve stent; B. Lateral view of valve stent; C. Delivery device.

an inflatable balloon. The valve stent is compressed onto the balloon of the delivery catheter using a mechanical crimping device. The balloon can be inflated to expand and release the valve stent which was used to replace the native aortic valve. The role of the hemostatic loader sheath is to ensure the positioning of the delivery catheter through the hemostasis valve of the 20F artery sheath. The stent delivery system can be classified into 20, 23, and 26 mm sizes, according to the diameter of the balloons.

*Animals*

Animal studies were approved by the local hospital ethics committee. All animals received care in compliance with the Guide for the Care and Use of Laboratory Animals (www.nap.edu/catalog/5140.html). Ten healthy sheep (five males and five females) weighing 25.16 ± 1.83 kg were used. Preoperative electrocardiography, chest radiography, and echocardiography (ECG) revealed no abnormality. Anesthesia was induced in the sheep with an intramuscular injection of ketamine (10 mg/kg) and maintained with intraoperative intravenous propofol ($0.2\ mg\cdot kg^{-1}\cdot min^{-1}$). All the sheep were monitored by performing ECG and oxygen saturation.

*Valve stent implantation*

The right femoral vein was punctured and we inserted a 6F leak-proof sheath, and 50 U/kg of heparin was administered. The temporary pacing lead was introduced into the apex of the right ventricle via the femoral vein sheath and then the pacemaker function was confirmed.

The left carotid artery was exposed and a 6F leak-proof sheath was introduced, and a 6F pigtail catheter was introduced into the ascending aorta for contrast medium injections. Aortic root angiography was performed to determine the best imaging position and measure the diameter of the aortic valve annulus (Fig. 2A). The type of valve stent was selected according to the diameter of the aortic valve annulus, and then it was compressed to the balloon of the delivery catheter by using a mechanical crimping device. The diameter of the selected valve stent should be 2–4 mm larger than the diameter of the aortic valve annulus.

The sheep were placed in a right lateral decubitus position. After the abdomen was opened, a 2 cm length abdominal aorta was exposed from the retroperitoneum and a 7F artery sheath was introduced. A stiff guide wire was advanced into the apex of the left ventricle via the 7F sheath under fluoroscopy (Fig. 2B). After the 7F sheath was withdrawn, a 20F artery sheath and inner dilator were inserted into the abdominal aorta over the stiff guide wire. Then, the inner dilator was removed and the 20F artery sheath was left in place. The delivery catheter equipped with the valve stent was threaded into the stiff wire and advanced into the descending aorta through a hemostatic loader sheath and the 20F artery sheath. Further manipulation and axial support with the deflection delivery catheter was required to cross the aortic arch and the native valve along with the stiff guide wire. When the valve stent was placed in the native aortic valve, aortic root angiography was performed (with 800-pis pressure and at 15 mL/s for a total volume of 20 mL) to determine the valve stent placement at the native aortic valve of the sheep by adjusting the depth of the delivery catheter.

Rapid right ventricular pacing (300 beats/min) was used to minimize pulsatile transaortic flow. Then the valve stent position was confirmed again using aortic root angiography (Fig. 2C). Under fluoroscopic guidance, the valve stent was expanded and released by injecting the balloon with dilute (10%) contrast agent (Fig. 2D). The contrast agent was extracted when the valve stent was fully inflated. Temporary pacing was stopped and the delivery catheter was extracted. The position and function of the artificial valve were observed by aortic root angiography (Fig. 2E and F).

*Postoperative treatment*

The delivery catheter, stiff guide wire, and 20F outer sheath were all removed. The abdominal aorta was sutured with 6–0 polypropylene suture material (Johnson and Johnson, New Brunswick City, NJ). The muscle and skin were then sutured after no errhysis was observed for three minutes. The pigtail catheter, temporary pace lead, and sheath on the carotid artery and femoral vein were all removed. A 7–0 polypropylene suture material was used for suturing the carotid artery. A 5-min compression hemostasis was applied at the puncture site of the femoral vein. All the sheep received postoperative intramuscular injections of penicillin and subcutaneous injections of heparin. Penicillin was administered for seven days to prevent infection, and then low-molecular-weight heparin and aspirin were administered for three and 60 days, respectively. The wound was disinfected daily with iodine. Sutures were removed at 6 days.

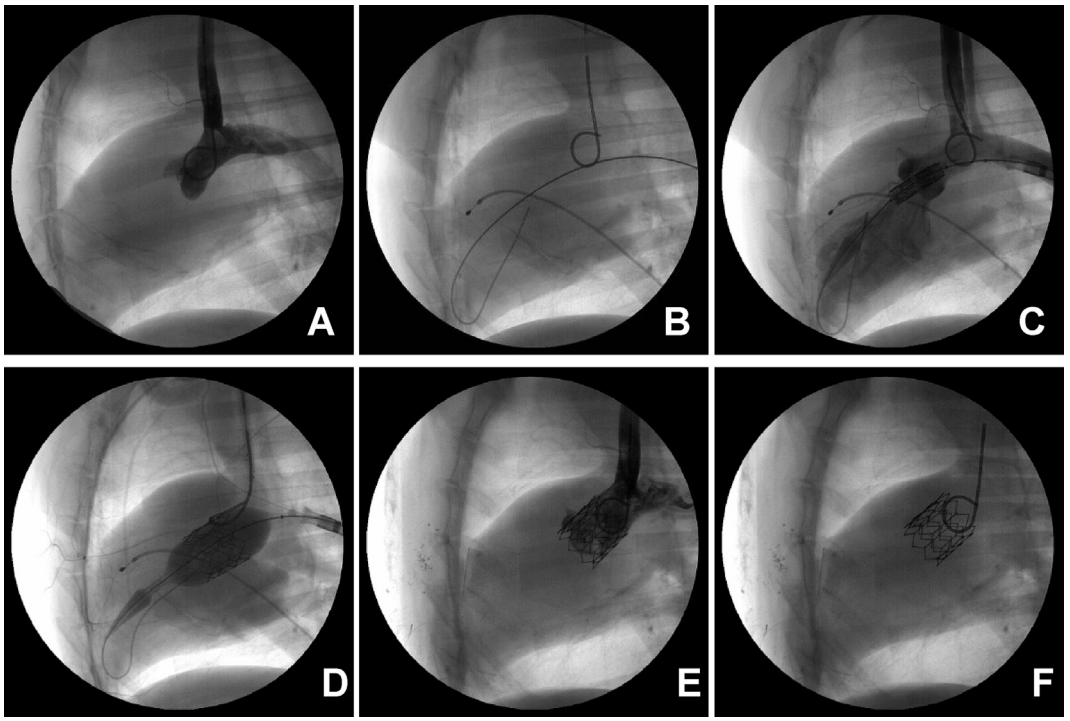


Fig. 2. Procedure of transcatheter aortic valve implantation. A. The angiogram of ascending aorta; B. A stiff guide wire was advanced into the apex of the left ventricle; C. Valve stent was placed in the native aortic valve; D. Valve stent was expanded and released by injecting the balloon with dilute contrast agent; E and F. The position and function of the artificial valve were observed on angiography after implantation.

*Evaluation of valve stent implantation*

The location and function of the artificial aortic valve were detected by aortic root angiography immediately after the operation. One randomly selected sheep was euthanized two hours after successful implantation for macroscopic inspection at necropsy. The general health status, including eating, defecation, and activity of the sheep were observed after the operation. The performance of the prosthetic aortic valve, including perivalvular leakage and aortic regurgitation, was evaluated based on findings from transthoracic echocardiography angiography six months after the operation. In addition, the function of the heart and hemodynamics of the artificial valve were observed. The prosthetic valve was examined macroscopically and histologically at six months after the operation.

*Statistical analysis*

Statistical analysis of all the data was performed by using SPSS 18.0 software (SPSS Inc., IL, USA). Measurement data were expressed as mean ± standard deviation (SD).

## Results

*Operation results*

Two sheep (No. 1 and No. 3) died of ventricular fibrillation during the operation because the higher position of the artificial valve affected the opening of the coronary artery. The valve stent implantation was completed in eight sheep. One sheep (No. 2) died of heart failure two weeks after the operation due to serious paravalvular leakage induced by the lower position of the valve stent. Autopsy showed that the valve stent was located under the aortic valve leading to serious paravalvular leakage. One sheep (No. 6) was sacrificed 2 h after successful implantation to observe the position and function of the valve. The cardiac anatomy of the sacrificed animal showed that the valve stent was well “anchored” against the aortic wall with an optimal position, the native aortic valves were stuck between the annulus and stent, no obstruction of coronary artery origins was observed, the lower edge of the valve stent was far away from the mitral valve, no tears of the prosthetic valve leaflets were apparent (Fig. 3).

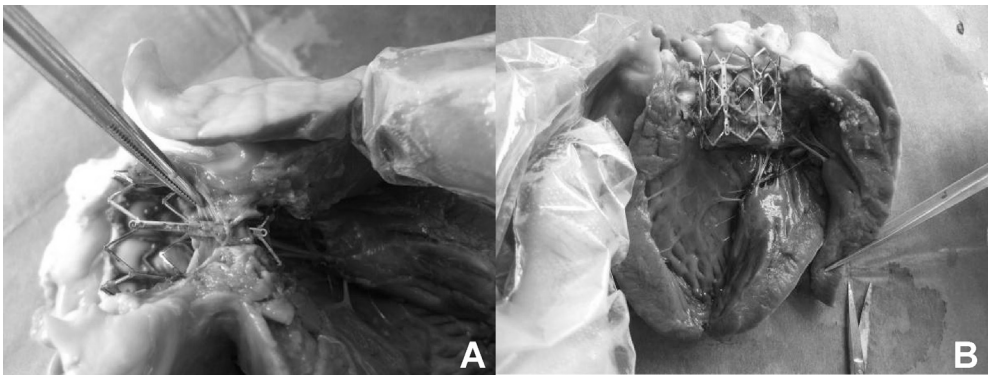


Fig. 3. Cardiac anatomy of sacrificed animal; A. Valve stent was well "anchored" against the aortic wall with optimal position; B. coronary artery origins and mitral valve were not affected.

Valve stents were implanted in the desired position in the remaining six sheep, no complications related to the operation occurred. Temporal sinus tachycardia occurred during implantation of the stent. No AV block was detected. The aortic root angiography revealed that the valve stent was implanted at a correct position and the switch function of the prosthetic aortic valve was normal, without significant regurgitation (Fig. 2E). The aortic annulus diameter was 21.88 ± 1.43 mm, the mean valve stent diameter of 24.5 ± 1.58 mm, the operation time was 104.30 ± 12.07 minutes, and the radiographic fluoroscopy time was 9.40 ± 2.41 minutes.

*Results at six postoperative months*

The six sheep survived for more than six months with normal diet and activity. Transthoracic color Doppler ultrasound at six postoperative months showed the normal position of the prosthetic valve and function of the artificial valve without obvious stenosis or insufficiency. The aortic valve stent did not affect the function of the mitral valve and its normal activities (Fig. 4). Angiography at six postoperative months revealed that the stent was at its location with full spread, without deformation and fracture, and that the artificial aortic valve had no regurgitation. The left and right coronary artery openings were not affected by the artificial aortic valve (Fig. 5). The H&E staining of the artificial valve leaflets at six postoperative months showed that the surface of the leaflet was smooth, without obvious cell or tissue infiltration (Fig. 6).

## Discussion

Recently, TAVI technology has developed rapidly and has been widely applied in the clinics. More than 100000 patients have received the TAVI treatment. TAVI is recommended as an alternative treatment method for severe stenosis in patients with a high risk of surgical operation.[4,5]

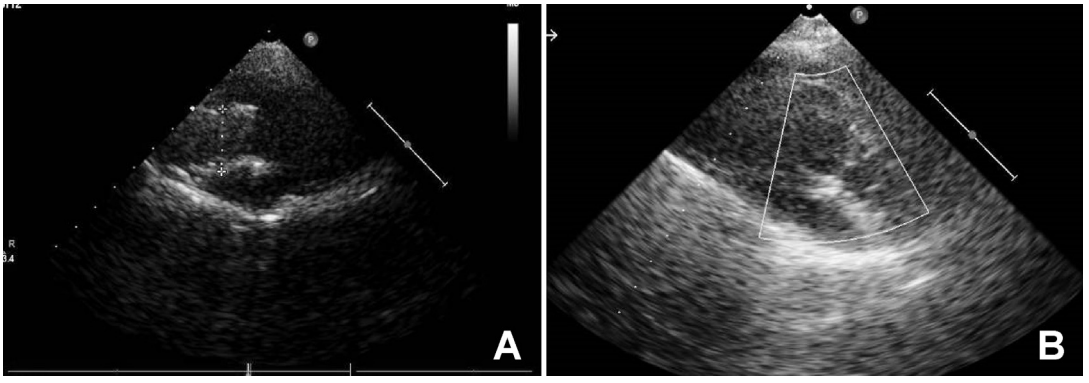


Fig. 4. Ultrasound at 6 months postoperative; A. Valve stent was located in the aortic valve. B. No regurgitation or paravalvular leakage was found.

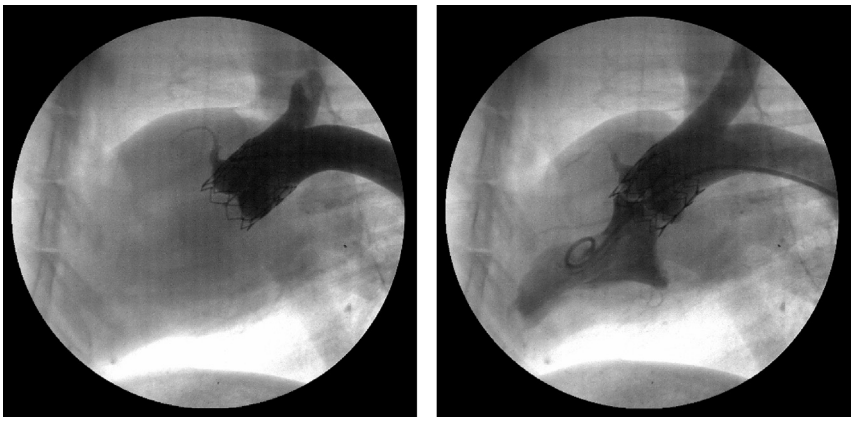

Fig. 5. Angiography at 6 postoperative months showed artificial aortic valve had no regurgitation.

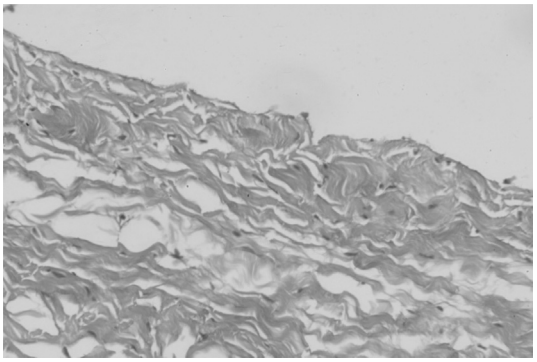

Fig. 6. Histological images of the artificial valve leaflets at 6 postoperative months showed the surface of the leaflet was smooth, without obvious cell or tissue infiltration.

*Prosthetic valve*

Cobalt-based alloy has good physicochemical properties, which allows it to be widely applied in medical and biological fields. First, the material shows good biocompatibility, no irritation to the recipient's body, which has been observed. Second, the material has a stable chemical performance and strong corrosion resistance. Third, it shows good mechanical properties with anti-fraying and fatigue resistance. Moreover, it has a low specific gravity and light quality for easy crimping and transportation.

Bovine pericardium as a biological valve has been applied in cardiac surgery. After treatment, the bovine pericardium shows good toughness and fatigue resistance performance, making it an ideal material for making artificial valves. Its surface performance is improved after sterilization, decellularized treatment, and calcification resistance. The polyester cloth that covers the dense stitching around the one-third segment of the stent was used as a gland pouch and effectively reduced the perivalvular leakage.

The artery sheath and delivery catheter are made of polytetrafluoroethylene with a hydrophilic coating. The myocardial and vascular smooth muscle are not easily damaged because of their smooth surface. The valve stent and ascending aorta should maintain a coaxial orientation during the stent implantation. The delivery catheter is characterized by the ability of its deflectable forepart; the function of deflection is accomplished by the rotation of the handle of the delivery catheter. This function made it easy for the stent to pass through the aortic arch and maintain the coaxial orientation with the ascending aorta, which is conducive to a steady release of the stent.

*Implantation access*

TAVI with transfemoral access is often preferred due to a perception of it being less invasive in an adult. However, the diameter of the femoral artery of adult sheep is only 4mm–5 mm which allows, at most, a 14F sheath to be inserted. The diameter of the abdominal aorta of an adult sheep is 7mm–8 mm which is relatively close to the average diameter of the femoral artery of adult humans. So the approach via the abdominal aorta was selected for transcatheter implantation of the valve stent in this animal study. The blood flow of the abdominal aorta would be completely blocked by a 20F artery sheath during a TAVI procedure via the abdominal aorta. Furthermore, It takes time to suture the puncture site of the abdominal aorta after the procedure. So we need to shorten the operating time, otherwise, avascular necrosis of both lower limbs may occur.

*Valve stent positioning*

The key factor of successful TAVI is to achieve an accurate position of the valve stent. The opening of the coronary artery is affected by the higher location of the stent, which might have led to myocardial infarction; whereas serious paravalvular leakage occurred as a result of the lower positioning of the artificial valve, which might have led to heart failure. Several points should be considered to accurately position the artificial valve, including the following: 1) The best angiography posture. The three aortic sinuses of sheep should be in the same line under angiography; which is necessary for accurate location of the valve stent. In the TAVI operation, the sheep was placed in a right lateral decubitus position, the posteroanterior position and a 5−10° cranio view were used in our study. The optimal angiography position was determined by performing angiography, with the aortic sinus in a straight line as the principle reference. 2) Rapid cardiac pacing. The aortic annulus is moving up and down too much within a normal heartbeat. Stent positioning at this time could not be accurate. High left ventricular pressure was produced by the great amount of the left ventricular blood flow due to the aortic valve orifice being clogged by the balloon of the expandable stent, which could lead to the balloon being "washed away". Rapid ventricular temporary pacing can slow down the velocity of blood flow from the left ventricle and reduce the motion amplitude of the aortic annulus.[6] The heart rate of the sheep is between 130 and 180 beats/min. Our experiment found that aortic pressure was significantly reduced by 250−300 beats/min of rapid pacing. The stent was released when the aortic pressure was decreased significantly, as confirmed by performing pressure monitoring after rapid temporary pacing. 3) Stent size. The diameter of the stent used was 2−4 mm larger than the diameter of the aortic annulus, in accordance with the principle of stent selection. Then if the valve stent achieved good expansion, it would closely adhere to the aortic annulus. 4) Stent releasing position. The artificial valve was sutured to the lower one-third segment of the stent. The accurate release position to cover the animal's native valve was at the lower one-third segment. That is, the lower edge of the stent was below the sinus; the distance from the lower edge to the sinus was 3−5 mm.

*Valve function*

Angiography and ultrasound observations at six postoperative months preliminarily indicated good performance of the artificial valve. A color Doppler ultrasound image confirmed the artificial valve with good open-and-close function, without significant stenosis or regurgitation. The hemodynamics examination indicated that the differential pressure across the artificial aortic valve was normal. All the results at six postoperative months indicated that the artificial valve could replace the native valve with good performance.

*Complications*

This study showed a high incidence of malpositioning of the valve stent compared with TAVI in aortic stenosis. Unlike calcific aortic stenosis, the normal aortic valve of sheep lacks fixation at the annulus during deployment, resulting in malpositioning. If the valve stent system is used to treat aortic stenosis, the incidence of malpositioning complications may be reduced. With TAVI in calcific aortic stenosis, perivalvular leak is noted in nearly all patients.[7] The reason is the poor coaptation between the stent and irregular calcium annulus which provides points for blood to leak back across the annulus into the ventricle. In this study, the valve stent were implanted in an optimal position and closely adheres to the smooth aortic wall in the normal aortic valve of the sheep. Additionally, the polyethylene terephthalate fabric covered portion of the stent can prevent blood from flowing back into the left ventricle. So little regurgitation or paravalvular leakage was observed in our experiment. Cobalt-based alloy materials were characterized by high hardness and high resistance to abrasion. No stent deformation or migration was seen in any of the animals at six months after implantation.

*Study limitation*

This study had several limitations. First, the number of animals was small and the follow-up time was short. Second, the TAVI was performed in healthy animals with normal aortic valves.

## Disclosures

There are no conflicts of interest to report.

## Acknowledgments

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