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An Integrated Pericardial Valved Stent Special for Percutaneous Tricuspid Implantation: An Animal Feasibility Study

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Background. **Various percutaneous valve replacement approaches have been reported in animals to replace the aortic and pulmonary valve. To broaden the indications of percutaneous approach to atrioventricular valves replacement, we developed a novel valved stent and evaluated the feasibility and safety of percutaneous implantation of the device in the tricuspid position.**

Materials and Methods. **A unidirectional semilunar valve of porcine pericardium was sutured to a valvular ring. Then the ring with pericardial valve was mounted on a double-edge nitinol stent to construct the tricuspid valved stent. Transcatheter tricuspid valved stent implantation was performed on 10 healthy sheep. These sheep were followed up shortly after procedure with echocardiography evaluation and 64-slice CT imaging examination during the periodical follow-up at 1 mo and at 6 mo post-implantation. Additionally, two sheep were sacrificed after the procedure for anatomic and histological evaluation one at 1 h and the other at 1 mo, respectively.**

Results. **Percutaneous valve implantation was successful in eight of 10 sheep. Two sheep died during the procedure due to migration of stent and fatal arrhythmia. The pressure of right heart did not significantly change after the procedure. Further echocardiography and imaging confirmed the stents were in desired position during the follow-up. The remaining six sheep with normal valvular and cardiac functionality survived for 6 mo after implantation.**

Conclusions. **The tricuspid stent with a valvular ring and pericardial valve can be implanted in tricuspid annulus percutaneous. The double-edge stent could substitute the native tricuspid valve chronically.**

Key Words: **valved stent; tricuspid valve; percutaneous.**

INTRODUCTION

Functional tricuspid regurgitation is a common valvular heart disease. In most cases, this is due to tricuspid annular dilatation secondary to mitral valve disease or some congenital heart diseases accompanied by pulmonary artery hypertension [1, 2]. Functional tricuspid regurgitation after mitral valvuloplasty sometimes continues to develop. The continuous progression of tricuspid regurgitation can overload the right ventricle chronically and lead to severe right heart failure, which is a delicate postoperative problem in patients who have undergone surgery for congenital heart diseases or mitral valve disorder [3].

Traditionally, in patients with intractable right-sided endocarditis, tricuspid valvulectomy is indicated [4]. The patients who underwent a Fontan procedure also can survived comfortably [5]. The absence of a tricuspid valve either following surgical excision or following right atrial connection to the pulmonary artery for the therapy of some congenital heart disease has been associated with survival, especially in patients with relatively normal right ventricles [4]. Valvuloplasty and valve replacement are recommended in patients with deterioration of their clinical status or signs of right ventricular dysfunction. However, patients who

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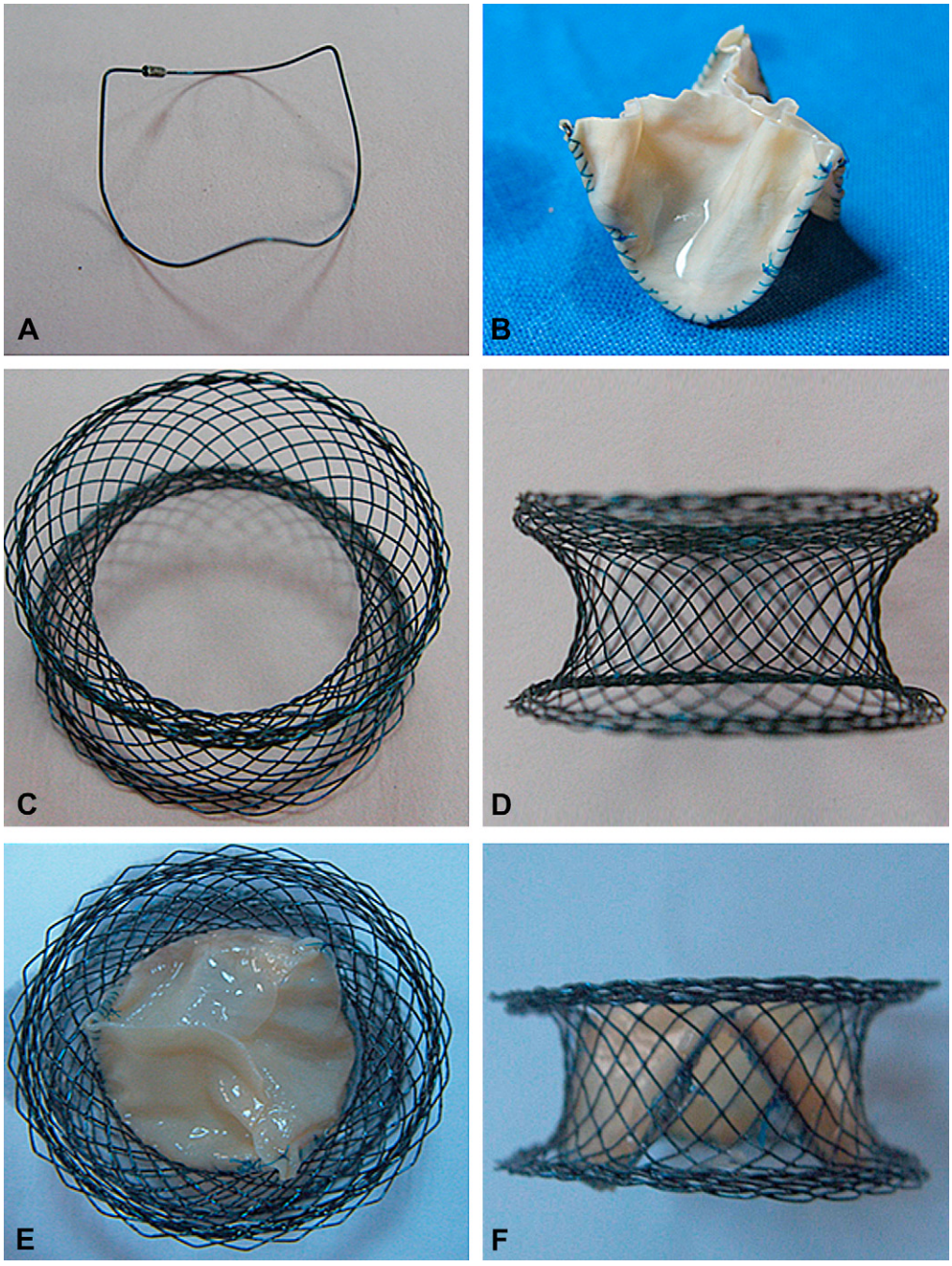

FIG. 1. Assembly of the valved stent. The nitinol valvular ring (A) was sutured with pericardial valve to form unidirectional trileaflet valve (B). The double-edge stent constructed from nitinol wire (C) en face view; (D) the lateral view. The valvular ring with pericardial valve was integrated to the stent (E: the ventricular side view of tricuspid stent; (F) the lateral view). (Color version of figure is available online.)

require tricuspid valve surgery are usually in an advanced stage of multivalvular disease, prior cardiac procedures, and other co-morbidities. So these associated diseases are the main cause of high morbidity and mortality of tricuspid valve surgery [6].

Percutaneous valve replacement is a less invasive procedure of treating valvular heart diseases. Transcatheter replacement of the pulmonary and aortic valve has been reported and many valved stents have been implanted in selected patients worldwide [7, 8]. Recently, interest has evolved to the implantation of atrioventricular valves by catheter [9, 10]. This study has designed and developed a nitinol stent with a valvular ring and a unidirectional semilunar valve made of porcine pericardium. We also validated the feasibility of percutaneous implantation of the valved stent in tricuspid position in healthy sheep with presumably normal hearts.

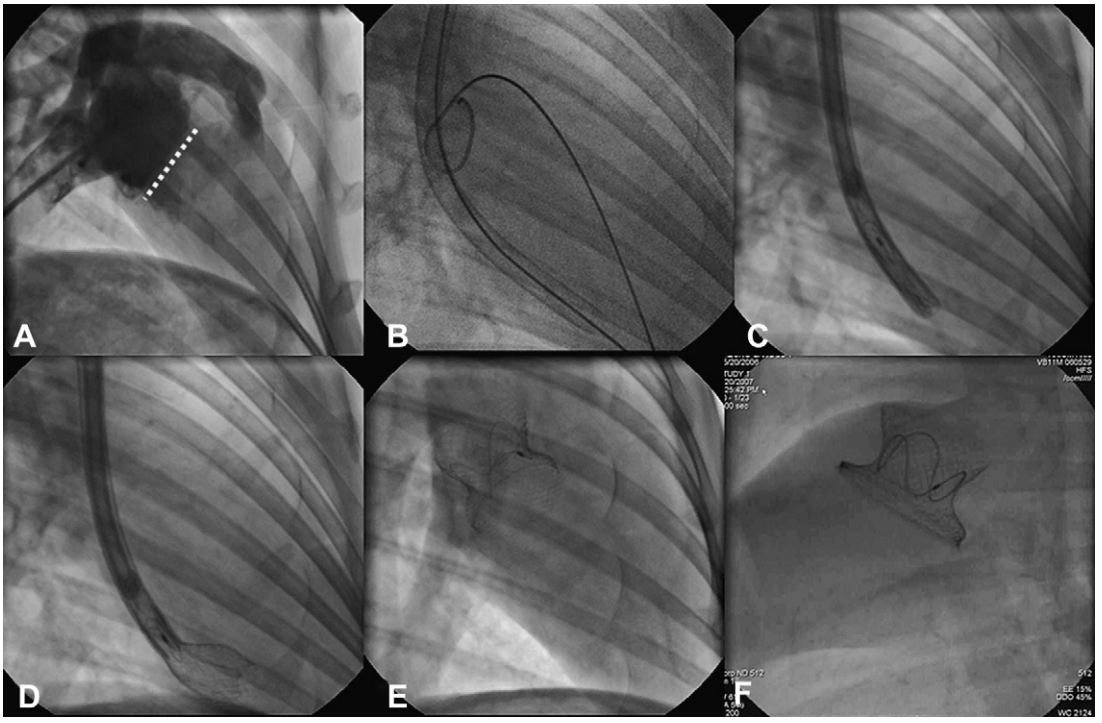

FIG. 2. The procedure of implantation under fluoroscopic Guidance. (A) The angiogram of right atrium at the right anterior oblique 27° and cranial 4° plane, the native tricuspid annulus became a line when the contrast eject to right ventricle from right atrium in right ventricular early-diastolic period. (The white dashed line designates the native tricuspid annulus). (B) The delivery system was advanced over a wire placed in the pulmonary artery. (C) The stent was pushed forward toward to the tricuspid annulus. (D) The stent's distal edge was first deployed gradually in the right ventricle. (E) The stent was completely deployed and anchored the tricuspid annulus. (F) View of the device from the left lateral projection after implantation.

METHODS

Design and Assembly of the Valved Stent

We developed a valvular ring constructed from a 0.25-mm nitinol wire (Fig. 1A). Three identical semilunar valve leaflets, which were tailored with fresh porcine pericardium cross-linked with a 0.6% glutaraldehyde solution, were mounted and sutured to the valvular ring with 7-0 Prolene (Fig. 1B). The formed unidirectional semilunar valve was then assembled to a double-edge stent constructed from a 0.18-mm nitinol wire (Shanghai Shape Memory Alloy Co. Ltd., Shanghai, China) (Fig. 1C and D). In order to select the suitable stent size based on the measurement of tricuspid annulus by transthoracic echocardiography (TTE) and angiography during the procedure, we developed different size stents with the waist diameter of the stent ranging from 22 to 26 mm. On the parasternal short axis plane of TTE, it was possible to visualize the tricuspid annulus and to measure the diameter of the tricuspid annulus. The whole device consisting of ring and stent was called tricuspid stent (Fig. 1E and F). *In vitro* valvular competency testing was performed as described [11].

Preparation of Animals

All animals received humane care in compliance with the Ministry of Science and Technology of the People's Republic of China Guide for the Care and Use of Laboratory Animals, and Principles of Laboratory Animal Care (NIH publication no. 86-23, revised 1985). All components of the experiments were approved by the institutional ethics committee. Ten healthy sheep (female 4 and male 6) weighing 25.0 to 27.8 kg received anesthetic induction with 0.01 mg/kg of atropine and 8 mg/kg of ketamine. General anesthesia was maintained with 2% pentobarbital. All procedures were performed in the dorsal recumbent position. Right external jugular and femoral veins were prepared for catheterization. ECG was routinely monitored throughout the whole procedure.

Transcatheter Tricuspid Stent Implantation

A 6F pig-tail catheter was advanced in the right atrium *via* the right femoral vein for atrial-graphy to identify the position and diameter of native tricuspid valve at a right anterior oblique 27° and cranial 4° plane. We usually selected a valved stent 2 mm larger than the diameter of the tricuspid annulus after annulus was sized by angiography. Then a super-stiff guidewire and multipurpose catheter were advanced in the pulmonary artery through the right external jugular vein, and the multipurpose catheter was exchanged for the 16F delivery catheter system (Shanghai Shape Memory Alloy Co. Ltd., China). The delivery catheter system consisted of an external sheath, dilated sheath, and a matched cable. Before the tricuspid stent was inserted into the delivery catheter system, the guidewire dilated sheath and cable were pulled out with the distal tip of external sheath preserved in the right ventricle. The tricuspid stent was hand-crimped into the proximal tip of external sheath. The tricuspid stent was pushed by cable in the external sheath under fluoroscopic guidance. When the distal edge was unsheathed in the right ventricle, the whole device was gently withdrawn until they sat against the tricuspid annulus by pulling back the external sheath and cable together. After proper positioning was confirmed by fluoroscopic and transthoracic echocardiography imaging, the waist and the proximal edge were unsheathed by pulling the external sheath in the annulus and right atrium, respectively, while maintaining the cable in position (Fig. 2). The 6F right heart catheter was advanced in the right heart and the pressure of right atrium and ventricle were measured before and after the

TABLE 1

Surgical Information of Implantations Performed on Experimental Sheep

ID	Tricuspid annulus echo (mm)	Tricuspid annulus angiography (mm)	Diameter of stent (mm)	Operation time (min)	X-ray exposure time (min)
1	18	19	22	67	9.2
2	18	17	20	56	10.7
3	16	17	20	77	12. 3
4	19	18	20	60	11.5
5	18	20	22	71	12.5
6	16	16	20	69	9.7
7	18	19	22	87	10.8
8	20	21	22	63	7.9
9	19	19	22	70	11.5
10	19	20	22	65	10.9
Mean	18.1	18.6	21.2	68.5	10.7
S.D.	1.3	1.6	1.0	8.8	1.4

operation. After the procedure, all sheep received postoperative intramuscular injections of penicillin and subcutaneous injections of low molecular weight heparins (2500 IU) for 3 days, and oral aspirin (3 mg/kg body weight) for 90 days.

Graft Retrieval and Histological Evaluation

After successful implantation, two animals were euthanized at 1 h and 1 mo, respectively, for graft retrieval and histological evaluation by cutting down the interventricular septum. The nitinol wire of the stent was carefully removed and the surface of nitinol wire was examined by scanning electron microscope (SEM). Testing of valvular competence was repeated *in vitro*.

Echocardiography, Computer Tomography (CT) Evaluation

The diameter of tricuspid annulus, the pressure of right atrium, right ventricular end-diastolic pressure, the degree of paravalvular leak, and tricuspid regurgitation were measured by transthoracic echocardiography (TTE) before and after the implantation. At the 1-mo and 6-mo postprocedure follow-up time-point, right ventricle function and hemodynamic function of the artificial valve were measured by TTE. The position of tricuspid stent was evaluated by 64-slice multi-slice CT (MSCT).

All statistical analyses were performed using commercially available software (SPSS version 11.0 for Windows; SPSS, Inc., Chicago, IL. A P value < 0.05 was considered significant.

RESULTS

Intraoperative Results and Clinical Follow-Up

Eight of 10 sheep had the tricuspid valved stent implantation. Two deaths occurred periprocedurally. One sheep died of ventricular fibrillation when the distal tip of external sheath was preserved in the right ventricle. We presumed the ventricular fibrillation was triggered by ventricular premature beats. The other sheep died because the tricuspid annulus was improperly sized, with the result of misplacement of the valved stent leading to acute circulatory failure. Unsustained ventricular tachycardia, ventricular, and atrial

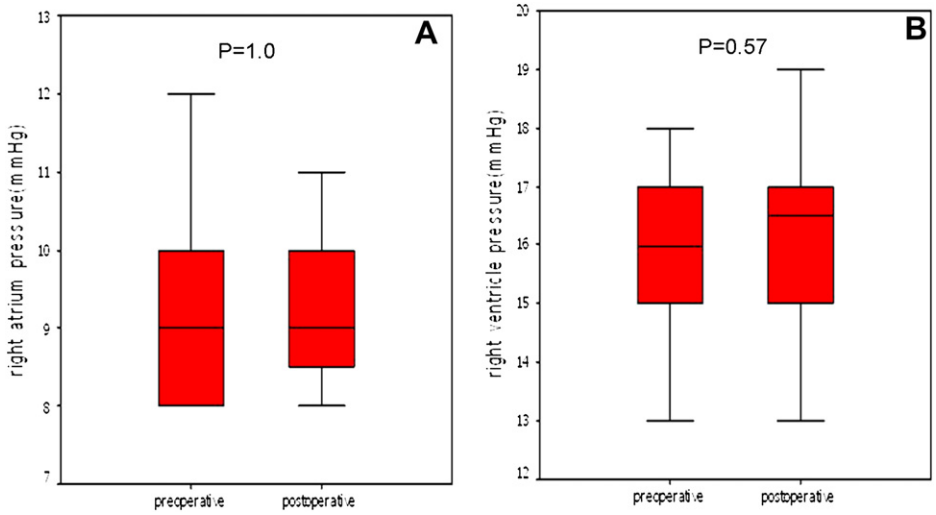

FIG. 3. Hemodynamic evaluation by right heart catheter. There was no significant difference in the pressure of right atrium (A) and right ventricle (B) between pre- and postoperation. (Color version of figure is available online.)

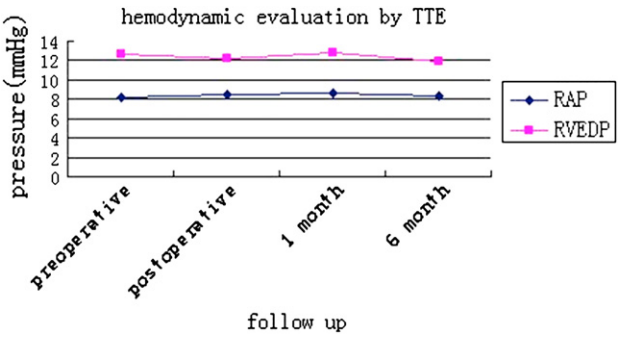

FIG. 4. Right heart pressures (mean in mm Hg) during follow-up. Good function of valve is shown by unchanged right atrial pressure and right ventricle end-diastolic pressure. (RAP: right atrial pressure; RVEDP: right ventricular end-diastolic pressure). (Color version of figure is available online.)

ectopic beats occurred during the procedure in all sheep. The measurement was obtained by angiography and Doppler ultrasound. The mean diameter of the tricuspid annulus was 18.6 ± 1.6 mm (range: 16 to 21 mm) and 18.1 ± 1.3 mm (range: 16 to 20 mm) as revealed by angiography and Doppler ultrasound, respectively. The best angiographic projection to visualize tricuspid annulus is the right anterior oblique 27° and cranial 4° plane. The mean stent diameter was 21.2 ± 1.0 (range: 20 to 22 mm). Mean surgery duration was 68.5 ± 8.8 min (range: 56 to 87 min). The mean X-ray exposure time was 10.7 ± 1.4 min (range: 7.9 to 12.5 min) (Table 1). Up to 6 mo follow-up, no significant persistence atrioventricular block and ventricular arrhythmia were observed. All the right heart pressures measured by right heart catheter between pre- and postoperation had no significant change (Fig. 3). The mean weight of the surviving animals increased 9.8 to 24.1 kg at 6 mo after the procedure. There was no significant increase in the pressure of the atrium and the ventricle measured by TTE (Fig. 4). No moderate to severe tricuspid regurgitation was observed. Paravalvular leakage was found on one surviving sheep with mild dyspnea at the 1-mo evaluation (data not shown).

Gross Anatomy and SEM Evaluation

Macroscopic findings at autopsy of the sheep showed that the native tricuspid valves were stuck between the annulus and stent at 1 h after implantation. The tricuspid stent anchored to the tricuspid annulus. The atrial edge of stent was far away from the coronary sinus. At 1-mo follow-up, macroscopic analysis showed that the whole device was still in the desired position and partially covered by a tissue layer (Fig. 5A and B). The position was consistent with the images of TTE and MSCT. No macroscopic damage, including the erosion of atrial wall, was noted in the right cavity. SEM photomicrograph of surface of the nitinol wire at 1 mo showed that there was a layer of endothelia (Fig. 5C). In addition, mild inflammatory cell infiltration was found in the histopathological examination of the pericardial valves (Fig. 5D). Fluid flow *in vitro* testing confirmed the pericardial valves could close and open normally again.

MSCT and Echocardiographic Evaluation

The CT image showed that the stents were good position which the proximal and distal edges were in the RA

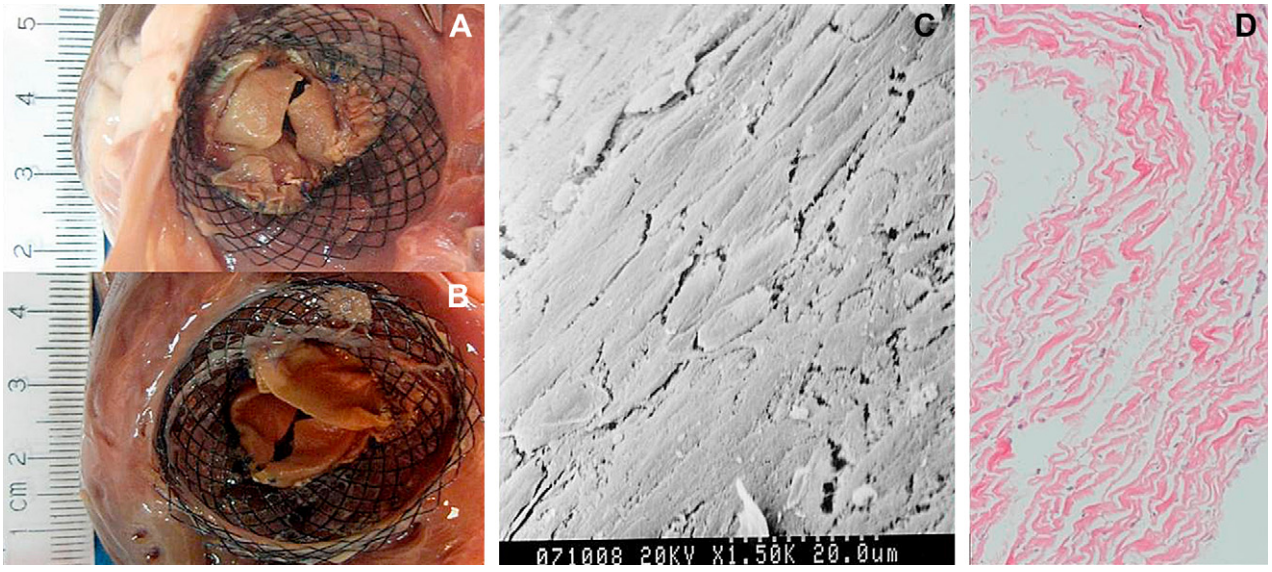

FIG. 5. The gross anatomy and scanning electron microscopic evaluation of the stent 1 mo after implantation. Macroscopic views demonstrated excellent position of the stent and the fibrous tissue began to cover the stent from atrial (A) and ventricular (B) sides. The scanning electron microscope photomicrograph showed that the surface of nitinol wire was covered by endothelia 1 mo after implantation (C). Inflammatory cell infiltration was found in the histopathological examination of the pericardial valves (D). (Color version of figure is available online.)

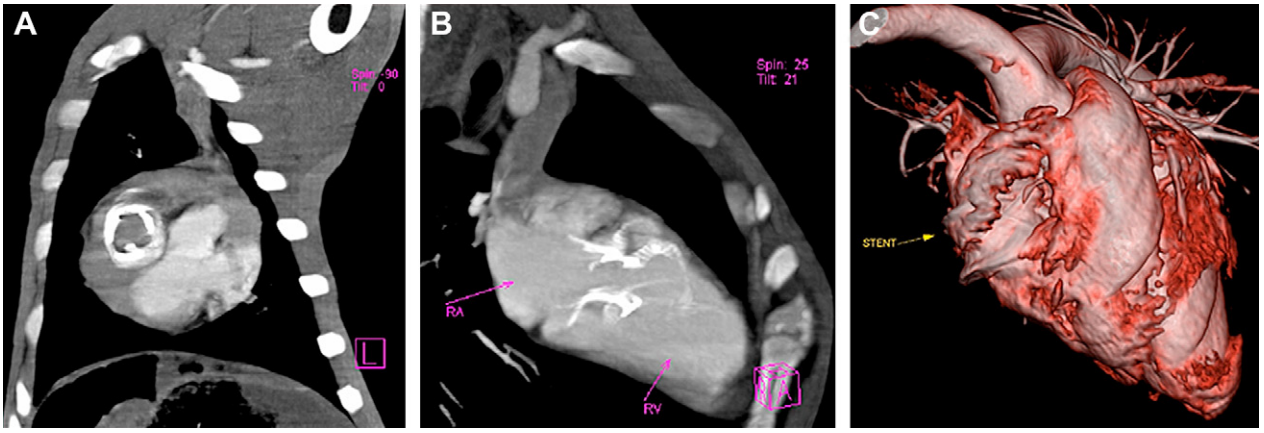

FIG. 6. The Image of multi-slice CT further confirmed the desired position of the valved stent at 3 mo after implantation. The images from the cross-section (A), long-axis (B), and three-dimensional reconstruction of multi-slice CT further confirmed the good position (C). (RV: right ventricle; RA: right atrium). (Color version of figure is available online.)

and the RV respectively (Fig. 6). The results suggested that the tricuspid stents were implanted accurately in the area of the tricuspid annulus. Echocardiographic imaging also showed that the tricuspid stents were in the desired position. The TTE image of the longest surviving sheep still showed a good position at 6-mo follow-up (Fig. 7).

DISCUSSION

Percutaneous valve replacement is a relatively new approach that is under evaluation at present [11–13]. Recently, Boudjemline and co-workers reported the percutaneous implantation of tricuspid stent [9]. New iterations of the valve and delivery system are under development. In this study, we produced a newly designed stent with a valvular ring and an integrated unidirectional valve made of porcine pericardium. Implantation of the device was found to be highly successful and efficacious at 6 mo post-surgery. One novelty of the present study was the design of valvular ring. In our initial experiment, we sutured the three semilunar pericardial valves directly onto the mesh of stent. Yet the stent failed to deploy freely because suture can limit the self-expanding performance. With the nitinol valvular ring, this new design avoided the disadvantage and improved sealing to reduce regurgitation. In addition, the valvular ring can enhance the support of stent. Another key improvement is the use of pericardium for prosthetic valve. In comparison with the use of natural valved venous segment reported in a recent study, the pericardium can be acquired more easily and the pericardial-made valve can be cut in different sizes to fit the actual annulus diameter. When three identical semilunar pericardial valves were sutured onto the valvular ring, three semilunar valves formed like native aortic valve. The prosthetic pericardium valve has shown excellent character in cardiac surgery over a long time, which implicated that our

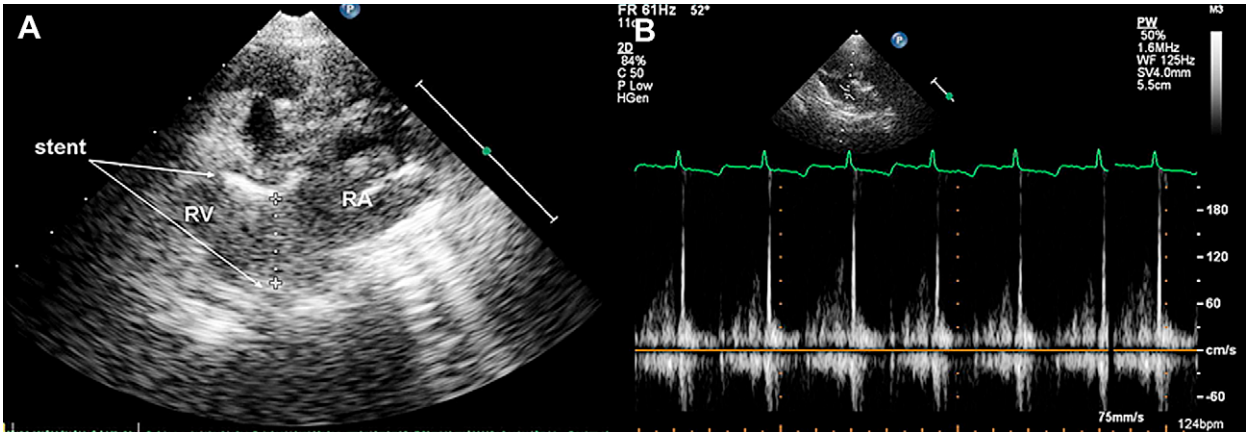

FIG. 7. Echocardiography showed the valved stent was in good position and had normal function 6 mo after implantation. The stent showed the strong echo signals (A). The continuous wave Doppler showed that the velocity of tricuspid valve was normal (B). (Color version of figure is available online.)

valved stent may be suitable for clinical use. Only one sheep was observed with paravalvular leak 1 mo after the procedure. The previous stent reported was covered by PTFE membrane, which was omitted in our design. However, we believed it was not necessary for the PTFE covering because the interspaces between the native annulus and the stent were filled by native valves and chordaes. The tricuspid native valve and chordaes inactivated by the stent reduced the opportunity for paravalvular leakage. We also felt that trivial paravalvular leak closed with progressive fibrosis on the foreign material and tightening of the annulus. Actually, there was only one paravalvular leak that occurred out of all eight stents implanted without PTFE covering. Moreover, without PTFE covering, the size of whole device could be easily reduced for inserting a compact delivery system as small as a 14F catheter, which was much smaller than previously reported. In contrast, we presumed the major reason for the paravalvular leak was the smaller size of stent selected. Therefore, identification of the correct position and actual size of native tricuspid annulus are critical when choosing a stent. Practically, we thought the best echo view for measurement was to observe the annulus in its parasternal short axis plane. In this view, the diameter of the annulus can be visualized and precise measurements made. We experienced the preferred angiogram of the right atrium was achieved at a right anterior oblique 27° and cranial 4° plane. In this position, the native tricuspid annulus became a line when the contrast ejected to the right ventricle from the right atrium in right ventricular early-diastolic period (Fig. 2A). The length of line was referred to the diameter of native tricuspid annulus and was also referred to the selected optional stent.

Study Limitations

First, although the sheep model used was similar to human anatomy, it differed in several critical features. In our study, there was no animal model for pathologic tricuspid regurgitation, for which this valved stent replacement may be useful. Specifically, human tricuspid incompetence results from annular dilatation in many cases with a tricuspid annulus between 30 and 40 mm, which is very different from the model used with annulus of 18 mm or less. So the size of stent should be larger for pathologic tricuspid regurgitation. In addition, the PTFE cover of the stent may be necessary to avoid paravalvular leak in the presence of such a larger tricuspid annulus due to pathologic tricuspid regurgitation. Second, the valved stent could not be completely retrieved once released. Thus, further modifications to the delivery system are needed to provide flexibility in cases of suboptimal placement and/or stent size incompatibility. Last, the animal cohort size was small and the follow-up time was short. The stent might compromise the A-V node. To avoid the disadvantage, we designed the left and right ventricle edge were only 6 mm larger than the waist. If the ventricular edge is excessively larger than the waist, the edge of stent might be in the proximity of conduction bundle and affect the conduction bundle. Additional studies, with larger cohorts and longer follow-up durations, are needed to evaluate atrial ventricular conduction and to provide sufficient reference data for potential clinical application.

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