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ORIGINAL RESEARCH - PRECLINICAL

A Novel Device for Tricuspid Regurgitation Reduction Featuring 3-Dimensional Leaflet and Atraumatic Anchor

Pivot-TR System

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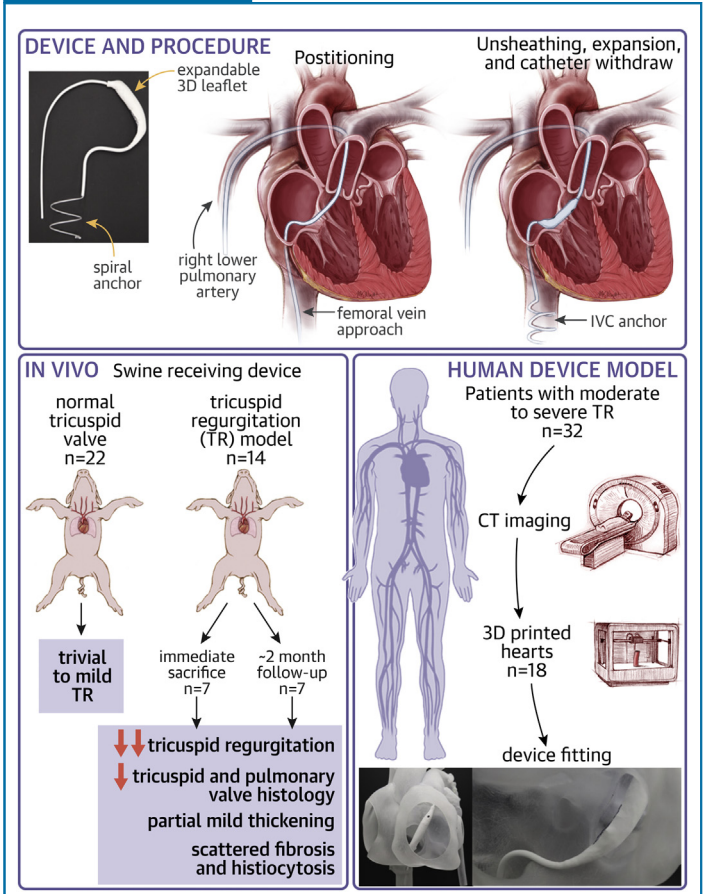
VISUAL ABSTRACT



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HIGHLIGHTS

- **The Pivot-TR is a novel transcatheter device for reduction of TR with the features of:1) vertical spacer; and 2) atraumatic anchoring system.**
- **The preclinical study up to 6 months of follow-up showed an encouraging safety and efficacy of the device.**
- **The Pivot-TR could provide an easy catheter-based solution for patients with severe TR.**
- **The current catheter-based TR treatments require sophisticated imaging guidance as well as relatively complex procedural steps.**
- **The Pivot-TR system may allow a simple procedure that can be done under fluoroscopy without requiring a complex learning curve.**

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ABBREVIATIONS AND ACRONYMS

AP = anteroposterior

CT = computed tomography

CTI = cavotricuspid isthmus

ePTFE = expanded polytetrafluoroethylene

IVC = inferior vena cava

RA = right atrium

RV = right ventricle

TR = tricuspid regurgitation

TV = tricuspid valve

SUMMARY

A new device called the Pivot-TR system was designed to treat tricuspid regurgitation with a novel spacer crossing the valve vertically. Its unique atraumatic anchoring system composed of both the elephant long nose and the inferior vena cava spiral anchor, in addition to the relatively easy implantation mechanism, enabled easy retrieval of the system later on. The system showed promising feasibility and safety results in this swine-based animal experiment, which should encourage human translation study. (J Am Coll Cardiol Basic Trans Science 2022;7:1249–1261)

Tricuspid regurgitation (TR) reduction therapy with catheter-based devices is challenging.[1] Recently, TR has been recognized as an important public health issue given that the human lifespan has expanded to 80 years or above, because the incidence of TR sharply soars at an age of 75 years and above and the overall prognosis of moderate or severe TR is very poor.[2] Unfortunately, surgical approach has not shown a good long-term outcome compared with mitral or aortic surgery, with a high postoperative mortality rate.[3,4] Among the device approaches, Edwards Forma (Edward Lifesciences)[5-8] is a device approach using a spacer for coaptation enhancement. The spacer can address a large coaptation gap of TR without requiring sophisticated imaging guidance, in contrast to MitraClip or Cardioband. However, the Forma system also has several drawbacks, such as risk from its traumatic anchor system to the right ventricle (RV) apex and maintenance needs for centerline orientation of the spacer in pursuit of a good clinical result. These shortcomings of the Forma spacer mainly derive from the coaxial orientation of the spacer. To overcome these limitations, we propose an intriguing concept of a novel spacer that has a feature of "vertically traversing" rather than "coaxially running through" the tricuspid valve (TV), without any traumatic invasive anchoring requirement.

METHODS

PIVOT-TR. The structure of the Pivot-TR. This device was made by Tau-PNU Medical Co, Yangsan, South Korea (Figure 1A). The Pivot-TR consists of 2 major parts. One is the pivot axis composed of the elephant nose and spiral anchor. A long preshaped nitinol wire (0.025-inch) serves as a backbone of the pivot axis from the elephant nose (200 ± 30 mm, 8.0 ± 0.5 F) through the inferior vena cava (IVC) spiral anchor. The other is the 3-dimensional (3D) leaflet having an expandable cylindrical mesh with outer expanded polytetrafluoroethylene (ePTFE) coated. The whole Pivot-TR system has a central lumen for the 0.035-inch guidewire. The whole device is covered by ePTFE.

The C curve-shaped pivot axis with shape-memory nitinol together with the spiral anchor was designed to provide the bracing effect of the pivot system into the target site without any invasive anchoring requirement (Figure 1B).

Regarding the 3D leaflets, a diverse length ranging from 50 to 100 mm and widths 9 mm, 12 mm, and 15 mm were tested in a nonhuman animal study.

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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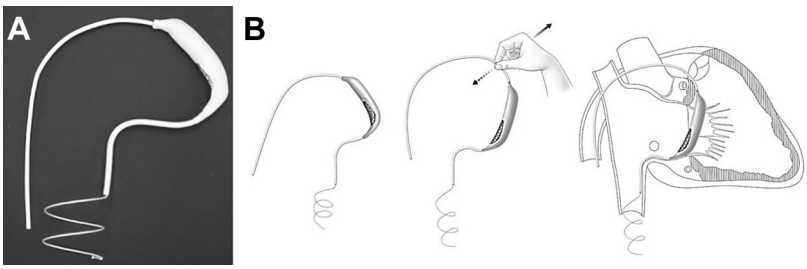
FIGURE 1 Structure and Mechanism of Pivot-TR Device



(A) The Pivot-TR consists of 2 major parts: the pivot axis composed of the elephant nose, and the spiral anchor. **(B)** The C curve–shaped pivot axis (shape-memory nitinol) with the spiral anchor was designed to provide the bracing effect of the pivot system into the target site without any invasive anchoring requirement.

The 3D leaflet has 2 windows on both sides of the spacer: a small one in the ventricular surface and the larger one in the atrial surface of the 3D leaflet, to allow blood flow communication into the inner cavity of the 3D leaflet.

The spiral anchor has a hook at its proximal tip for snare retrieval later on. The diameter of the anchor tested in the animals was 35 mm.

The procedure of the Pivot-TR. All procedures were performed mainly under fluoroscopy guidance. Transthoracic echocardiographic monitoring was used to guide the position of the 3D leaflet. A 19-F introducer sheath was inserted in the right or left femoral vein. The 5-F curved pigtail was placed in the main pulmonary artery and the 0.035-inch guidewire was introduced through the pigtail catheter and subsequently directed to the right lower pulmonary artery. The pivot system was delivered over the 0.035-inch guidewire up to the point of the collapsed 3D leaflet crossing the TV. The delivery catheter of the pivot system was gently unsheathed to allow the 3D leaflet to expand, and further unsheathing of the delivery catheter was performed to allow the spiral anchor to be deployed in the IVC. At this moment, the 7.5-F pusher catheter was used to keep the 3D leaflet in its intended position. If the position of the pivot system was found to be suboptimal, the whole pivot system was recaptured into the delivery catheter and repositioned. Once the Pivot-TR system was in the optimal position, the pivot system was disconnected through the delivery system by pulling out the 0.035-inch guidewire and releasing the nylon thread or conventional snare (Gooseneck Snare [EV3] or Ensnare [Merit Medical Systems]) attached to the proximal hook of the spiral anchor.

ANIMALS. All animals were handled in accordance with the NIH guideline and Animal Care and Use Committee policies of the Pusan National Yangsan University Hospital (PNUYH), and all animals received humane care. All experimental protocols and studies were approved by the Institutional Review Board of the PNUYH (IRB no. 2021-007-A1C0[0]).

A total of 60 pigs (Yorkshire farm swine, weight 43.9 ± 4.0 kg) were used in this study. For the initial design development phase, 24 animals were used for the development of a 3D leaflet[9] (data not shown here). Subsequently, 36 animals were used for the Pivot-TR's proof of concept both with normal TV (n = 22) or with destroyed TV (n = 14) either on nonsurvival or on survival experiments.

All survival animals were given 20 mg rivaroxaban daily during the survival periods. All animals were killed at the end of the experiments. The hearts and adjacent organs were thoroughly inspected and the specimens were sent for histopathologic examinations.

Creation of TR model. TR was created by the destruction of the valve structure under fluoroscopic guidance (Integris H5000F, Philips Medical Systems). Both snare catheter (Ensnare or Gooseneck Snare) and 0.014-in guidewire from the superior vena cava or IVC were intentionally delivered into the RV cavity and then snared the 0.014-inch guidewire in the RV cavity to form a loop. If the loop was found to entangle the subvalvular structure of the TV, it was forcefully pulled out to destroy the valve. This maneuver was repeated until chordal rupture or flail motion of the leaflet was confirmed by means of echocardiography.

Nonsurvival and survival experiments. ***Normal valve group (n = 22).*** In the normal valve group, a total of 11 animals were used to confirm the procedural feasibility of the Pivot-TR. The devices were implanted and subsequently followed for up to 6 months to verify the interaction between the

Pivot-TR and the native TV (n = 11 swine: 2 at 1-week follow-up, 3 at 1-month follow-up, and 2 each at 2-month, 3-month, and 6-month follow-up).

Destroyed TR model group (n = 14). Among all destroyed TR models, immediate outcome studies were performed in 7 animals and then midterm follow-up studies (n = 7) were performed as follows: 1 at 2 weeks, 5 at 2 months, and 1 at 4 months of follow-up. Regarding follow-up periods, besides initial design verification (<2 weeks of follow-up), 2-month follow-up was set as a standard period because rapidly growing animals' hearts during longer follow-up could be a confounding factor of outcome. In an animal that had moderate TR after Pivot-TR, a 4-month follow-up was performed as an exception.

IMAGING ANALYSIS. Fluoroscopic examination. We technically verified the procedural success for the TR pivot device by means of X-ray fluoroscopy (Integris H5000F, Philips Medical Systems)

Transthoracic echocardiography. The GE Vivid q ultrasound was used for transthoracic echocardiographic imaging. TR grading was mainly determined with the use of color Doppler images by mutual agreement of 2 ultrasonography specialists. TR was graded into 5 categories: 1 = mild; 2 = moderate; 3 = severe, 4 = massive; and 5 = torrential.

Computed tomography. Five swine (1 each at 1-month, 3-month, and 4-month follow-up, and 2 at 6-month follow-up) among the survival experiments (n = 18) were randomly selected to undergo contrast-enhanced cardiac computed tomography (CT) with the use of a 128-detector dual-source system (Somatom Definition Flash, Siemens Healthineers).

GROSS AND PATHOLOGIC EVALUATION. The devices and tissues were sent to a laboratory for tissue preparation (Genoss Co). An independent and experienced pathologist of the Pusan National University Hospital examined the specimens.

VISUAL EVALUATION OF THE PIVOT-TR FUNCTION WITH HARVESTED HEART ON A MECHANICAL PUMPING SYSTEM. Each harvested heart with either functional or destroyed valve was put on a homemade mechanical pumping system for direct visualization of beating leaflet motion with the 3D leaflet. The functional TR model was created by increasing the right heart chamber pressure above 780 mm H_2O.

PIVOT-TR FOR HUMAN TRANSLATION WITH THE USE OF PRINTED 3D HUMAN TR HEARTS. For human translation, a total of 18 hearts with moderate or severe TR before undergoing TR surgery were printed using consecutive preoperative cardiac CT images (n = 32) from the Pusan National University Yangsan Hospital from 2012 to 2020. In this human heart printing, the pulmonary artery and IVC were also included. Moreover, the Pivot-TR was applied in these printed hearts to find out how to adjust the design of Pivot-TR. The power needed to mobilize the 3D leaflet out of its therapeutic plan was measured after the pivot was applied to the printed heart (Figure 2).

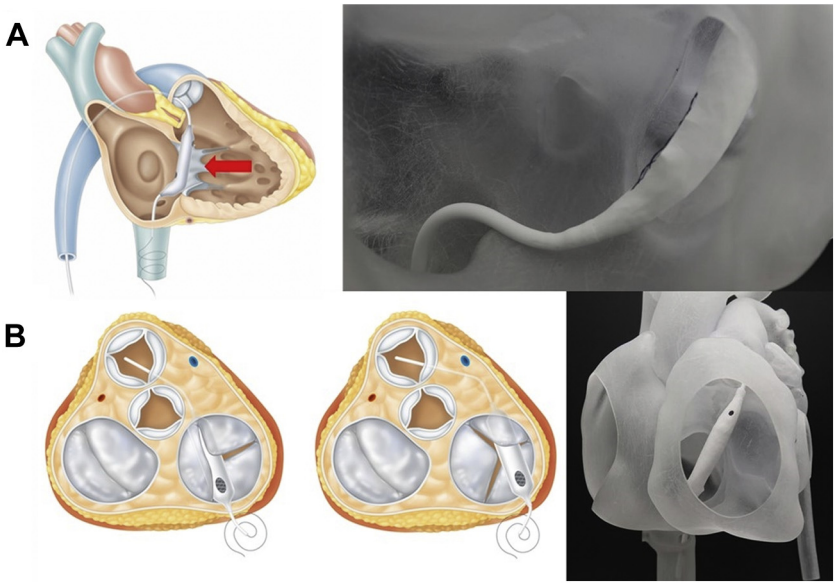
STATISTICAL ANALYSIS. In this paper, some data are summarized as mean ± SD. For the analysis of the echocardiographic findings data of the destroyed TR model, because the data were ranked and small in number, nonparametric tests (Wilcoxon signed rank tests for the nonsurvival experiments and Friedman tests for the survival experiments) were performed. When the nonparametric tests were used, data were summarized as median (IQR). In the case of the survival experiments with the Friedman test results, we performed the Nemenyi test to compare each follow-up time with baseline. All statistical analyses were conducted with the use of the Statistical Package for the Social Sciences (IBM SPSS Statistics for Windows, version 21.0, 2012, IBM) and R (R Statistical Software for Windows, version 4.1.1, 2021, Foundation for Statistical Computing) along with the R package PCMCRplus. A P value of <0.05 was considered to be statistically significant.

RESULTS

PIVOT-TR PROCEDURE. In all cases, the Pivot-TRs were successfully deployed in the target sites. All procedures were performed under fluoroscopic and transthoracic echocardiographic guidance. The main delivery mechanism was a simple withdrawal of the delivery catheter for unsheathing so that the 3D leaflet and spiral anchor would expand out. There were no procedure-associated complications in all cases. Before the final release of Pivot-TR, repositioning of the 3D leaflet was possible by recapturing the Pivot-TR system with the delivery catheter and then unsheathing it again (Figures 3A to 3E).

RETRIEVAL TESTS OF PIVOT-TR. In 17 animals, retrieval of the Pivot-TR was attempted right after the immediate procedure (n = 14), 2 weeks after the procedure (n = 2), or 4 weeks after the procedure (n = 1) with conventional Gooseneck or Ensnare systems. Retrieval was performed by grabbing the proximal tip of the IVC spiral anchor with a snare and simply pulling out the whole Pivot-TR system to be exteriorized through the 19-F femoral vein sheath. Immediately after the procedure and 2 weeks after the procedure, all devices were successfully retrieved through 19-F femoral vein sheaths without causing

FIGURE 2 **3D Printed Heart Bench Test for Human Translation**



The anteroposterior (AP) direction movement is designed to withstand well, while the lateral movement is designed to move well. The tension needed to move the 3D leaflet by 10 mm was **(A)** 200.5 ± 47.2 mm Hg in the AP direction and **(B)** 70.5 ± 32.2 mm Hg in the septolateral direction.

any damage. Post-retrieval echocardiography showed no abnormality caused by the Pivot-TR system or retrieval procedure. But retrieval was not possible at 4 weeks after the procedure in this swine model owing to the tight adhesion of spiral anchor systems to IVC walls (Figures 3F and 3G).

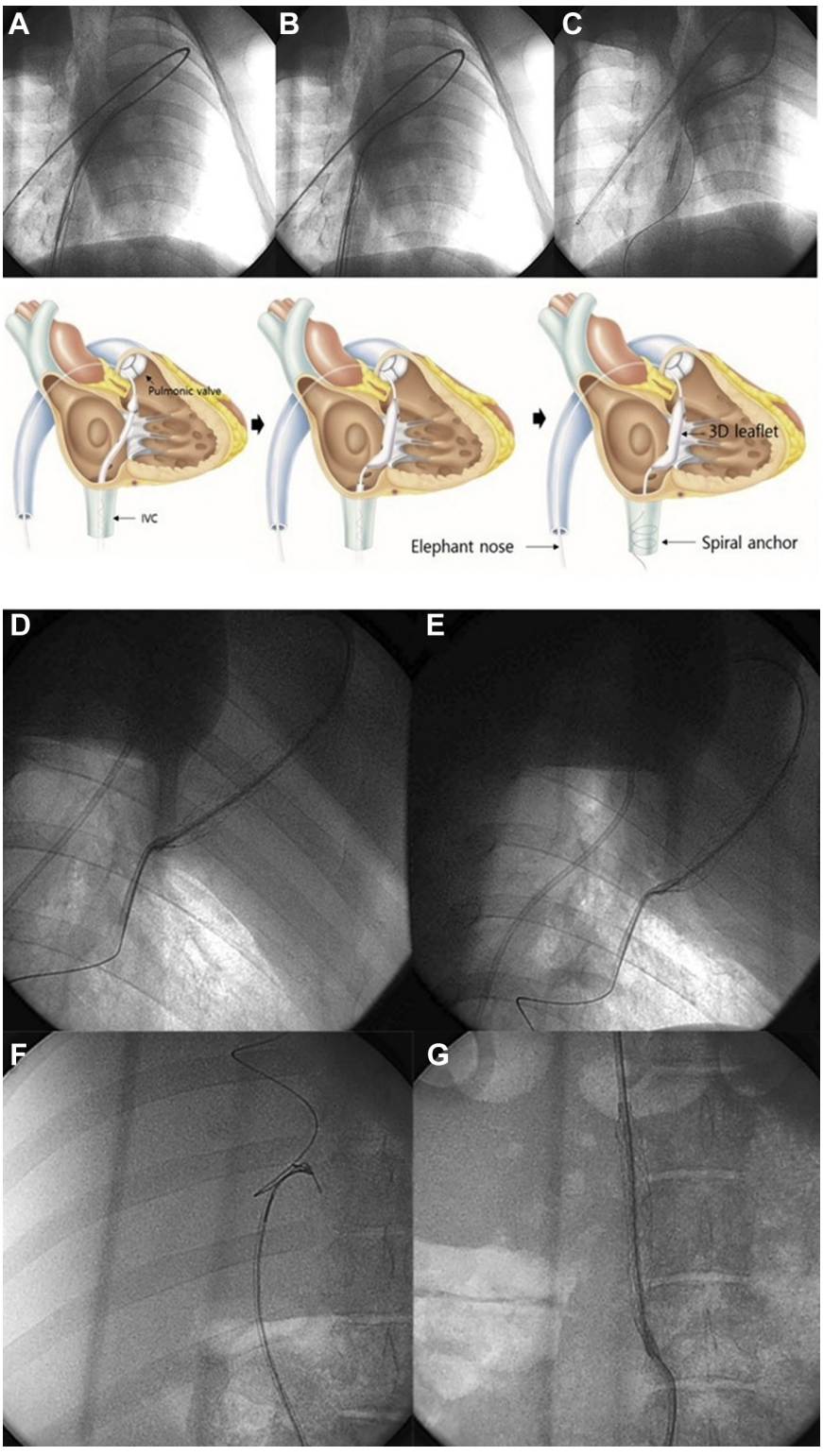
ECHOCARDIOGRAPHIC FINDINGS. In all of the animal experiments, there were no cases of significant flow obstruction in tricuspid inflow or RV outflow as indicated by flow acceleration on color flow Doppler. Pulmonary valve function was normal except for 1 case of mild pulmonary valvular regurgitation (0.028%). Focal mild thickening of native tricuspid leaflets especially close to the septal commissure was observed in most cases of survival experiments. Mean tricuspid valve inflow pressure gradient was 1.33 ± 0.48 mm Hg (n = 11), and mean pulmonary valve systolic pressure gradient was 1.0 ± 0.0 mm Hg (n = 2) in randomly measured CW Doppler data.

Normal TV. The Pivot-3D leaflet was interacting with surrounding native leaflets without any significant impairment on normal leaflet function. Only trivial or mild TR at a site of contact between Pivot-3D and native leaflets was observed in all animals. All 3D leaflets maintained their original position without significant migration that could result in any alteration of the valve function (Figures 4A and 4B).

Destroyed TR model. In nonsurvival experiments (n = 7), the Pivot-TR system showed significant TR reduction (TR grade median: baseline 3 [IQR: 2-4] to postprocedure 1 [IQR: 1-1]; $P = 0.035$). In survival experiments (n = 7) with torrential TR and destroyed TR models, compared with baseline (TR grade median 5 [IQR: 4.5-5.0]), significant TR reduction was observed for most of the follow-up periods: immediately postprocedure (1 [IQR: 1.00-1.25]; $P = 0.004$), 2 weeks (1.5 [IQR: 1.0-2.0]; $P = 0.017$), 1 month (1.75 [IQR: 1.125-2.000]; $P = 0.047$), and 2 months (2 [IQR: 1.625-2.000]; $P = 0.059$) (Figures 4C to 4G).

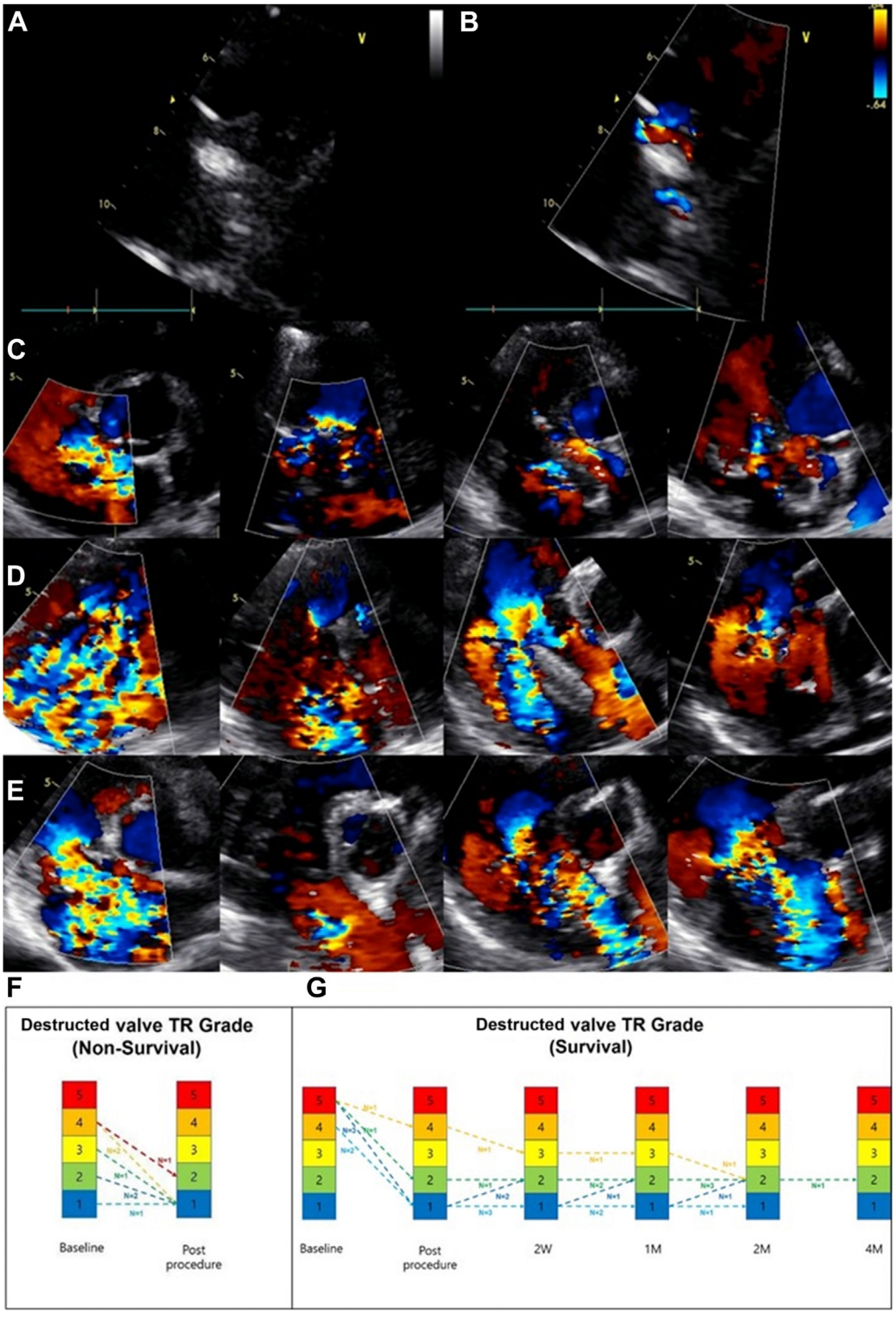
NECROPSY FINDINGS AND HISTOPATHOLOGY IN SURVIVAL EXPERIMENTS. All animals killed at the end of the survival experiments underwent thorough necropsy. All Pivot-TR systems had clean tissue coverings on visual estimation. Mild thickening of native leaflets was observed especially at the zone of septal commissure where the native leaflet had chronic deformity such as folding or wrinkling due to continuous contact with the Pivot-3D leaflet. The spiral anchor of the IVC showed no abnormal deleterious effect on the IVC. One animal showed a focal outbulging segment of the IVC at the focal isthmus zone of the IVC communicating with several hepatic veins, which is peculiar to swine anatomy.

FIGURE 3 Procedures of the Pivot-TR



(A to C) Procedural steps for Pivot-TR implantation. **(D)** Final position of Pivot-TR immediately postprocedure and **(E)** at 3-month follow-up. **(F, G)** Retrieval of the Pivot-TR after 2 weeks. IVC = inferior vena cava.

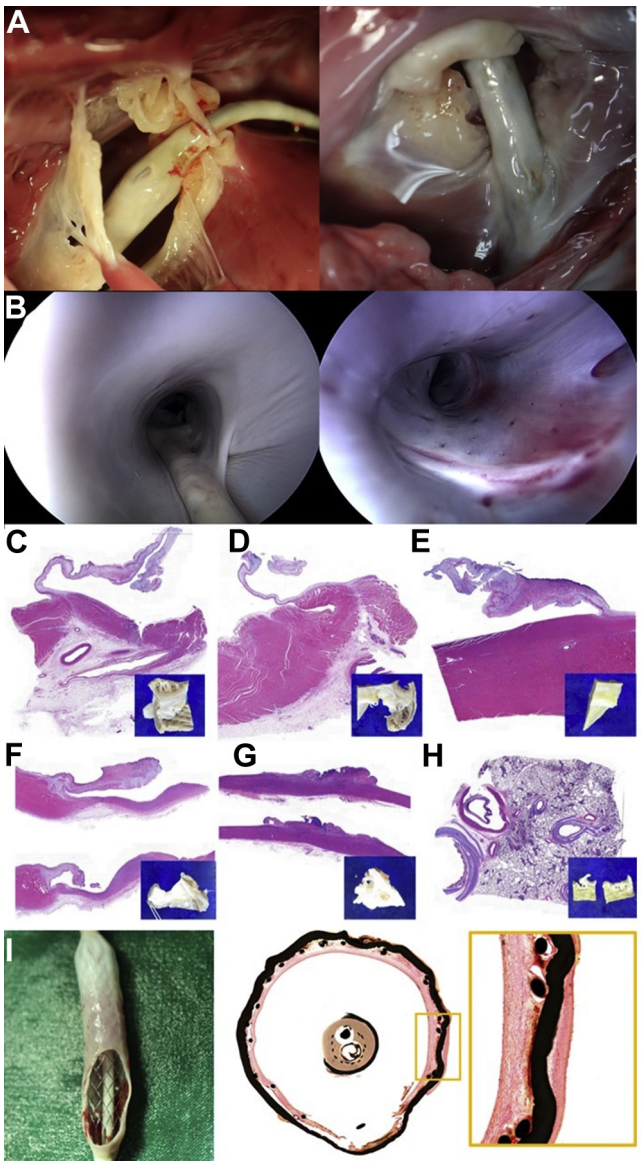
FIGURE 4 Echocardiographic Results



(A, B) Pivot-TR device in normal valve after 24 weeks. **(C to E)** Tricuspid regurgitation (TR) reduction in destroyed valve: **(C)** baseline immediately postprocedure, **(D)** after 1 month, and **(E)** after 2 months. **(F)** TR reduction in normal valve (TR grade). **(G)** TR reduction in destroyed valve (TR grade). 1 = mild; 2 = moderate; 3 = severe; 4 = massive; 5 = torrential.

JACC: BASIC TO TRANSLATIONAL SCIENCE VOL. 7, NO. 12, 2022
DECEMBER 2022:1249–1261

FIGURE 5 Gross and Pathology Results After 24 Weeks of Implantation in Swine



(A) Pivot-TR and tricuspid valve (TV) and **(B)** inferior vena cava. **(C)** Posterior leaflet of TV, **(D)** anterior leaflet of TV, **(E)** septal leaflet of TV, **(F)** pulmonary valve, **(G)** Pulmonary artery, **(H)** right lung, and **(I)** 3D leaflet (spacer) of the Pivot-TR device (9 weeks).

HISTOLOGIC FINDINGS. The catheter originated from the IVC, running into the right atrium (RA), RV, pulmonary artery, and intraparenchymal artery of the lung. The 3D leaflet was adherent to the endocardium between the posterior and septal leaflets. The heart was bisected along an imaginary midline between the coronary sulcus and apex.

The leaflets were relatively unremarkable, and the posterior leaflets of the TV were generally intact. The 3D leaflet was covered by neointima that was adherent to the endothelial surface between posterior and septal leaflets. Microscopically, the posterior leaflet maintained general architecture. The anterior leaflet was unremarkable in the lateral aspect. The area around it met the septal leaflet and showed thickening and nodularity. Microscopically, the lateral portion was thickened at the tip of the valve. The septal leaflet was mildly thickened. The surface showed fibroblastic and histiocytic reactions with subendothelial fibrosis, and the 3D leaflet portion of the catheter lay at the junction of posterior and septal leaflets forming sheath. Microscopically, the leaflet was thickened, the distal portion showed myxoid degeneration, and the neointima exhibited fibrosis and calcification but no active inflammation.

The pulmonary valve was slightly thickened with fibrosis, and hemosiderin macrophages were observed in the subendothelial area. The intrapulmonary artery along which the catheter ran was unremarkable. On the pulmonary arterial endothelium at 30 mm above the pulmonary valve, a small nodular lesion was observed measuring <10 mm. The lesion was formed in the intima and consisted of marked fibroblastic and histiocytic reactions and fibrotic stroma.

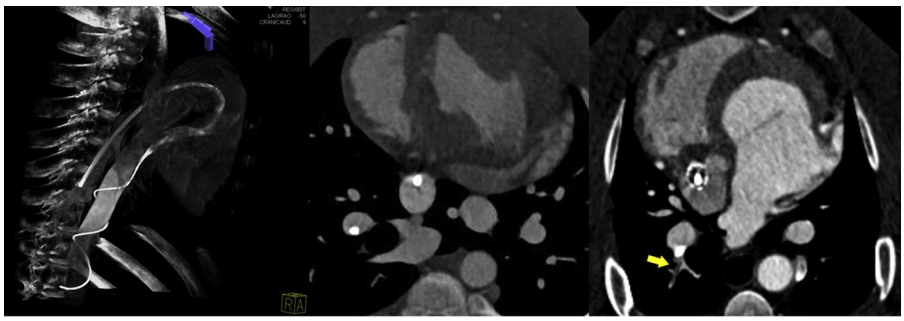
Lung artery and parenchyma were unremarkable. The neointima was formed around the catheter. It was fibrotic with histiocytic reactions at the surface. The lung parenchyma did not show inflammation, and the catheter was anchored in the IVC. The IVC and liver parenchyma were grossly unremarkable. The liver was grossly and microscopically unremarkable (Figure 5).

CT FINDINGS. Among the survival animals, 5 were randomly selected to check the CT findings during follow-up. Average follow-up at the time of CT scan was 16.2 ± 8.38 weeks. There was 1 case showing a minor nonocclusive thrombus in the distal pulmonary artery (Figure 6). Otherwise, no abnormal finding was found.

VISUAL ESTIMATION OF THE INTERACTION OF PIVOT-TR WITH SURROUNDING NATIVE TRICUSPID LEAFLETS WITH HARVESTED SWINE HEARTS ON MECHANICAL PUMPING SYSTEMS. The Pivot-3D leaflet was positioned between surrounding leaflets without impairing the leaflet function in normal TV and contributed to blocking the regurgitant orifice in the partially destroyed tricuspid valve model (Figure 7).

PIVOT-TR COMPLICATIONS. One case (5.6%) showed device infection at 2-month follow-up, which might have been a procedure-related infection judging from the timing. There were no cases of TV inflow

FIGURE 6 Computed Tomography after 24 Weeks of Implantation in Swine



Yellow arrow indicates minor nonocclusive thrombus in the pulmonary artery.

obstruction or RV outflow tract obstruction. Mild pulmonary regurgitation was observed on echocardiography in 1 animal in the survival experiments with concomitant mild thickening of the pulmonic valves. One case of nonocclusive minor pulmonary arterial thrombus was observed in the CT scan of 1 of the animals randomly selected for CT. In 2 cases, hepatic vein occlusive thrombi extending to the RA were found in survival experiments. Although these 2 cases had inappropriately long 3D leaflet spacers that eventually blocked the hepatic vein inflow orifice into the IVC lumen, the finding could not rule out that the spacer itself might be associated with the thrombus generation. There was no case of significant device migrations, with all 3D leaflets preserving their position of vertically traversing through the TV.

PIVOT-TR FOR HUMAN TRANSLATION. Based on our analysis of human CT data (n = 32), the Pivot-TR device for human trial will have various size components to better conform the patient's anatomy (cavotricuspid isthmus [CTI] length: 20/30/40/50 mm; 3D leaflet height: 50/60/70/80/90 mm; 3D leaflet width: 9/12/15 mm; spiral anchor diameter in IVC: 30/35/40 mm).

A total of 18 hearts were 3D printed with the use of consecutive preoperative cardiac CT images (n = 32) for human translation test. The tension needed to move the 3D leaflet by 10 mm was 200.5 ± 47.2 mm Hg in the anteroposterior (AP) direction and 70.5 ± 32.2 mm Hg in the septolateral direction. When these 2 result values were compared, the force required to move in the AP direction appeared to be greater and was statistically significant ($P < 0.001$) Thus, the AP direction movement is designed to withstand well, while the lateral movement is designed to move well.

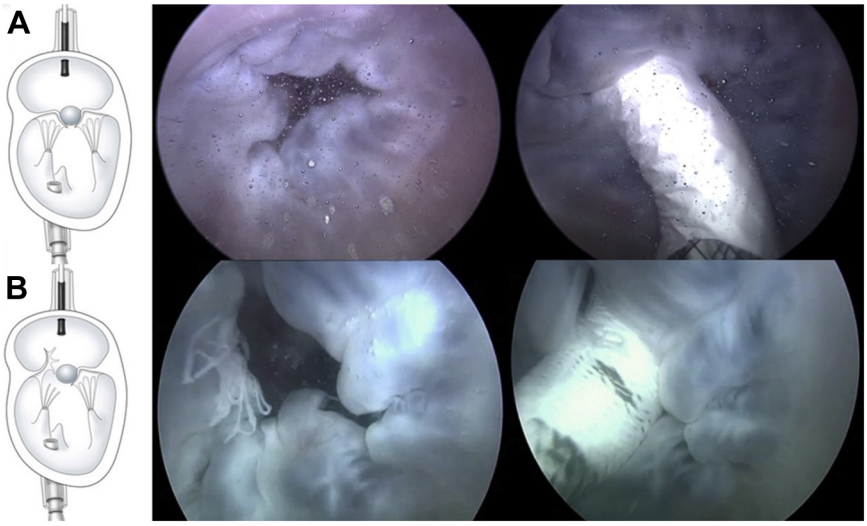
DISCUSSION

In this animal study, we found that the Pivot-TR can be positioned without any traumatic anchoring system in the target site and can maintain its intended original position without RV outflow tract or tricuspid inflow obstruction. The Pivot-TR system showed several features in this study, as follows.

First, it has a nontraumatic anchor using a preshaped nitinol backbone-based elephant nose and the IVC spiral anchor, the so-called pivot axis. It is well known that any type of invasive anchoring or equivalents in the dilated and frail RV actually could lead to severe complications, as was observed with Forma and Cardioband. The preshaped arch type of nitinol backbone of the pivot axis system is designed to embrace the path along the pulmonary artery, supraventricular crest of the RV, TV, RA, and, subsequently, toward the IVC. In our bench model experiments, an average of 201.0 ± 45.3 mm Hg RV systolic pressure was needed to displace the 3D spacer out of its therapeutic boundary (AP movement of the 3D membrane). This embracing biomechanics accounts for the long-term securing of device position without any evidence of migration in animal experiments.

Second, the procedure of the Pivot-TR was remarkably easy, taking <30 minutes (data not shown) without requiring any sophisticated imaging guidance such as transesophageal echocardiography or intracardiac echocardiography. The simplicity of the procedural imaging guidance would apparently enable the procedure to be done under conscious sedation or alert condition in human trials. In the current TR device treatments, such as MitraClip or Cardioband, time-consuming procedures with

FIGURE 7 Isolated Swine Heart Pump Simulator



(A) Regurgitant orifice and Pivot-TR application in functional tricuspid regurgitation model. **(B)** Regurgitant orifice and Pivot-TR application in destroyed tricuspid regurgitation model.

complex imaging guidance are the most cumbersome limitations. The Pivot-TR confers a clear advantage in this regard. Moreover, the easy retrieval of the device must be an important safety advantage because acute postprocedure RV overload due to a sudden block of TR may lead to fatal RV failure in some cases.[10-15] Pivot-TR device retrieval was possible for up to 2 weeks in our study. The time window of 2 weeks in the swine model may correspond to 1 to 2 months in humans, because swine tissue reaction is known to be 6 times faster than that of humans.[16,17]

Third, the 3D leaflet of the Pivot device had the advantage of a spacer that can cover up even a huge coaptation gap with or without leaflet tethering that is beyond the capability of annuloplasty or edge-to-edge repair.[18] The diameter of the 3D leaflet is 9 mm, 12 mm, or 15 mm in our current design. It was encouraging to observe that even the huge TRs caused by the intentional destruction of subvalvular structures were also responsive to the Pivot-TR system with significant TR reduction. The Pivot's 3D membrane has a vertical and oblique orientation crossing the TV annular plane (a vertically traversing spacer) and is positioned between the septal and anteroposterior leaflets. The TR orifice is known to have an oval shape with a longer vertical axis rather than a circular shape.[19] Thus, the vertically traversing spacer may better match the regurgitant orifice than a coaxial spacer like that of the Forma device. According to the experimental data conducted in the human 3D heart print model, the structure of the pivot is more likely to move mediolaterally rather than in the AP direction, and, supported by the experimental results through the harvested heart on a pump simulator, it is expected to be easier to be located in the center of regurgitant orifice owing to interactive action with the surrounding native valves.

The 3D leaflet has fenestration windows (open type) on the RA surface that allows blood communication into the inner cavity of the 3D membrane, which may mimic the healing mechanism of the left atrium appendageal closure device.[20] Our study group already verified the neo-endocardial covering of the 3D membrane without the fenestration window. However, we found that the open type had more favorable tissue covering such that the open type 3D membrane has become our final design (comparative data are not shown here). But, the risk of thromboembolism would be presumably higher in the open type than the closed type.

Fourth, with Pivot-TR application on printed human 3D heart models, we found that the most important variable of device design is the CTI length, ranging from approximately 20 to 50 mm depending on the size of the RA. Other factors included the height of the 3D membrane (50-70 mm) and the diameter of the spiral anchor (25-40 mm). These 3 factors may become the determinant of customized Pivot-TR design together with the width of the 3D leaflet depending on the coaptation gap. The alignment of the IVC to the line of

the RA to the pulmonary artery will be a little different according to the patient's anatomy and influences the Pivot-TR system's alignment to some extent. In our experiments with 18 printed human models with diverse heart sizes and anatomy, it seemed that there was no case of the Pivot-TR showing worrisome deviation of the 3D membrane in the TV area. However, that needs to be verified in human trials.

The concept of the vertically traversing 3D leaflet can also be applied on the platform of mitral loop cerclage, in which the 3D space is attached on the RV arm of the CSTV instead of the pivot axis. This would be intriguing because it could have the potential to treat both mitral regurgitation and TR at once.[21]

POTENTIAL COMPLICATIONS OF THE PIVOT-TR. In terms of native leaflet response to the artificial 3D leaflet membrane, the parts of leaflets around the septal commissure showed mild thickening after 6 months of follow-up, without deleterious effect but with trivial to mild TR. This may trade off the device's benefit to some extent. Any device contacting the leaflet itself results in some alteration of leaflet structure, for example, the leaflet fusion in edge-to-edge TR repair. However, this finding cannot deny that the human Pivot-TR may come up with more serious damage on the TV or pulmonic valve, especially with longer follow-up than 6 months.

Migration of the 3D leaflet may occur. Moreover, in response to TR reduction, later RA and RV volume reduction may have a certain effect on 3D leaflet function. A study reported that TR device treatments led to approximately 10% volume reduction in the right heart within 1 month without any further change later on.[22] The change of RV volume may be mainly associated with the free wall of the right heart rather than the septal part. It was also an interesting finding that, in our animal study, 23.0% $\pm$ 0.2% change of body weight (this could be correlated with heart size change) during follow-up did not result in any significant change of 3D leaflet function.

The unique design of the Pivot-TR system has nothing to do with the conduction block and is less likely to have a constraint impact on RV contractility because it does not touch the RV myocardium directly.

Pulmonary thromboembolism or small branch occlusion may be associated with the Pivot-TR. Although ePTFE is best known for thromboresistant biomaterial, in our study, mild nonocclusive thromboembolism was seen in a peripheral pulmonary artery. It was not clear whether this thrombus originated from the open-type spacer or represented in situ thrombus formation by the local flow disturbance All pigs were administered 20 mg Xarelto (rivaroxaban) daily for anticoagulation. Perhaps warfarin would be a better option to prevent thromboembolic events in human trials. A shorter elephant nose that does not reach out to the far distal branch of the pulmonary artery may help to further prevent this complication.

Elephant nose–related significant pulmonary valve damage was not observed in our study except for mild pulmonary regurgitation.

Device infection may occur.

Damage to the IVC may occur due to the spiral anchor or during the procedure. In our study, the spiral anchor was well positioned in normal segments of the IVC. In Carillon, the size of venous anchor is recommend to be around 1.5 to 2.0 times larger than the vein size.[23] In our experiments, the spiral anchor diameter was 35 mm in all experiments, which might have been over up to 3 times larger than that of the baseline IVC diameter, given the assumption of swine IVC average diameter of 9.9 $\pm$ 0.7 mm.[24] However, in the human translation of this study, the spiral anchor diameter needs to be customized according to each IVC size.

STUDY LIMITATIONS. First, the animal TR model in this study was made by destruction of the valvular structure. Therefore, the TR reduction of Pivot-TR in humans may differ. However, the functional TR might come up with better results with the Pivot-TR system owing to better-coordinated interaction with the surrounding intact leaflet, as was inferred through our observation of the Pivot-TR in normal valves. On the other hand, our study also carried a potential limitation of studies coming from acute TR model wherein dilation of the TV annulus may limit the effectiveness of the device. Also, the Pivot-TR may be less effective in cor pulmonale–associated TR.

Second, TR severity was estimated only by visual evaluation by echocardiographic specialists, without any objective parameter. In swine models, echocardiographic evaluation has several limitations due to the difficulty of imaging acquisition in diverse angles.

Third, in swine models, anatomic structure from pulmonary artery through IVC is somewhat different from humans. The most prominent difference is that the CTI of the RA is almost negligible in pigs whereas humans have a very prominent CTI (normal average 25 mm). Moreover, the more severe the TR, the longer the CTI; it may reach out as long as 50 mm to 60 mm according to our printed 3D human heart models. Therefore, Pivot-TR devices need to be customized to each case's anatomy. In out printed human 3D heart experiments ($n = 18$), we found that 4 variables were crucial for human applications: CTI length (20, 30, 40, and 50 mm), 3D leaflet height (50, 60, and 70 mm), 3D

leaflet width (9, 12, and 15 mm), and diameter of IVC anchor (25, 30, 35, and 40 mm).

CONCLUSIONS

In this preclinical study, the Pivot-TR device demonstrated a novel concept of the TR device taking advantage of the anatomic continuous line from pulmonary artery to IVC with a vertically traversing spacer through the TV. With this unique design, the procedure was able to be performed simply and easily, and TR reduction was effective and durable. Human translation is strongly warranted.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Pivot-TR has the potential to overcome previous shortcomings of the spacer with the following 2 major features: 1) a vertically traversing spacer through the tricuspid valve for better matching the geometry of the human functional regurgitant orifice; and 2) an easy delivery system without requiring any traumatic invasive anchor.

TRANSLATIONAL OUTLOOK: A future study needs to confirm these promising results in clinical trials.

REFERENCES

1. Asmarats L, Puri R, Latib A, Navia JL, Rodés-Cabau J. Transcatheter tricuspid valve interventions: landscape, challenges, and future directions. *J Am Coll Cardiol*. 2018;71:2935–2956.

2. Enriquez-Sarano M, Messika-Zeitoun D, et al. Tricuspid regurgitation is a public health crisis. *Prog Cardiovasc Dis*. 2019;62:447–451.

3. Vassileva CM, Shabosky J, Boley T, Markwell S, Hazelrigg M. Tricuspid valve surgery: the past 10 years from the Nationwide Inpatient Sample (NIS) database. *J Thorac Cardiovasc Surg*. 2012;143:1043–1049.

4. Kim JB, Jung SH, Choo CH, Chung CH, Lee DW. Clinical and echocardiographic outcomes after surgery for severe isolated tricuspid regurgitation. *J Thorac Cardiovasc Surg*. 2013;146:278–284.

5. Curio J, Demir OM, Pagnesi M, et al. Update on the current landscape of transcatheter options for tricuspid regurgitation treatment. *Interv Cardiol*. 2019;14:54–61.

6. Perlman G, Praz F, Puri R, et al. Transcatheter tricuspid valve repair with a new transcatheter coaptation system for the treatment of severe tricuspid regurgitation: 1-year clinical and echocardiographic results. *J Am Coll Cardiol Intv*. 2017;10:1994–2003.

7. Asmarats L, Perlman G, Praz F, et al. Long-term outcomes of the Forma transcatheter tricuspid valve repair system for the treatment of severe tricuspid regurgitation: insights from the first-in-human experience. *J Am Coll Cardiol Intv*. 2019;12:1438–1447.

8. Maurizio T, Rebecca TH, Hannes A, et al. The International Multicenter Trivalve Registry: which patients are undergoing transcatheter tricuspid repair? *J Am Coll Cardiol Intv*. 2017;10:1982–1990.

9. Chon MK, Shin DH, Jung SJ, Park HJ, Kim JH. A percutaneous catheter solution as a spacer for regurgitant heart valve disease. *Coatings*. 2021;11:926–932.

10. Andrej A, Natalya M, Marta K, et al. Predicting right ventricular failure after LVAD implantation: role of tricuspid valve annulus displacement. *J Cardiothorac Vasc Anesth*. 2020;34(5):1204–1210.

11. Lawlor M, Kampaktsis P, Wang V, et al. Incidence and predictors of cardiogenic shock following tricuspid valve repair or replacement. *J Am Coll Cardiol*. 2020;76(17 suppl S):B212.

12. Baran DA, Grines CL, Bailey S, et al. SCAI clinical expert consensus statement on the classification of cardiogenic shock. *Catheter Cardiovasc Interv*. 2019;94:1–9.

13. Jentzer JC, Diepen S, Barsness GW, et al. Cardiogenic shock classification to predict mortality in the cardiac intensive care unit. *J Am Coll Cardiol*. 2019;74:2117–2128.

14. Schwartz RS, Holmes DR, van Tassel RA, et al. Left atrial appendage obliteration mechanisms of healing and intracardiac integration. *J Cardiothorac Vasc Anesth*. 2010;3:870–877.

15. Estrada VHE, Franco DLM, Moreno AAV, Gambasica JAR, Nuneza CCC. Postoperative right ventricular failure in cardiac surgery. *Cardiol Res*. 2016;7:185–195.

16. Conn PM. *Sourcebook of Models for Biomedical Research*. Springer Science and Business Media; 2008.

17. Chaabane C, Otsuka F, Virmani R, Piallat MLB. Biological responses in stented arteries. *Cariovasc Res*. 2013;99:353–363.

18. Scholotter F, Orban M, Rommel KP, et al. Aetiology-based clinical scenarios predict outcomes of transcatheter edge-go-edge tricuspid valve repair of functional tricuspid regurgitation. *Eur Heart J*. 2019;21:1117–1125.

19. Song JM, Jang MK, Choi YS, et al. The vena contracta in functional tricuspid regurgitation: a real-time three-dimensional color Doppler

echocardiography study. *J Am Soc Echocardiogr*. 2011;24:663–670.

20. Nakase M, Asami M, Yahagi K, et al. Autopsy findings of left atrial appendage closure device. *Cardiovasc Pathol*. 2022;56:107384.

21. Park YH, Chon MK, Lederman RJ, et al. Mitral loop cerclage annuloplasty for secondary mitral regurgitation: first human results. *J Am Coll Cardiol Intv*. 2017;10:597–610.

22. Rommel K-P, Besler C, Thilo N, et al. Physiological and clinical consequences of right ventricular volume overload reduction after transcatheter treatment for tricuspid regurgitation. *J Am Coll Cardiol Intv*. 2019;12:1423–1434.

23. Hijazi ZM, Jeldman T, Cheatham J, Sievert H. *Complications During Percutaneous Interventions for Congenital and Structural Heart Disease*. CRC Press; 2013.

24. Wan-Yin S, Shuang W, Lan-Yue H, et al. Swine model of thrombotic caval occlusion created by autologous thrombus injection with assistance of intra-caval net knitting. *Sci Rep*. 2016;5:18546–18554.

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