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PRECLINICAL RESEARCH

Percutaneous caval stent valve implantation: investigation of an interventional approach for treatment of tricuspid regurgitation

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Aims Severe tricuspid regurgitation (TR) reduces cardiac output (CO) and increases central venous pressure leading to secondary organ dysfunction. To date, the open surgical approach is the only option to treat TR. Herein, we report our experience of treatment by percutaneous implantation of valved stents in the inferior vena cava (IVC) and superior vena cava (SVC) to substitute tricuspid valve function in a model of acute insufficiency.

Methods and results Acute TR grades III–IV was created in 13 sheep (54–75 kg) via papillary muscle and chordae avulsion using a 0.07 inch wire blade. Successful creation of TR was confirmed using angiography and by a prominent ventricular wave in central venous pressure recording. Two self-expanding nitinol stents containing a porcine pulmonary valve were then implanted in the IVC and SVC in a transcatheter approach. Implantation was performed through the right jugular vein by means of a 21 F catheter and guided by fluoroscopy. Haemodynamics were continuously monitored and valve function was verified by angiography and epicardial echocardiography. After successful implantation and proof of concept in the acute study (acute group, $n = 9$), chronic studies were ($n = 4$, 4 weeks follow-up) performed. Tricuspid regurgitation grades III–IV was successfully created in all animals and resulted in a significant reduction of CO. A ventricular wave in the IVC of 16.2 ± 2.33 mmHg (acute group) and 14.9 ± 1.71 mmHg (chronic group) confirmed the presence of severe TR. After deployment of the IVC and the SVC valve, the ventricular wave in the IVC significantly decreased to 13.9 ± 2.97 mmHg (acute group) and 12.7 ± 1.15 (chronic group), whereas CO significantly increased to 4.20 ± 0.84 L/min (acute group) and 5.4 ± 0.67 L/min (chronic group). At autopsy, correct device position was verified in all successfully implanted animals, no macroscopic damage resulting from the implantation procedure was observed.

Conclusion In high-grade tricuspid insufficiency, percutaneous implantation of valved stents in the central venous position reduces venous regurgitation and improves haemodynamics in the animal experiment. Implantation of one or two valves in central venous position is technically feasible. Functional replacement of the insufficient tricuspid valve leads to an increase in CO. This technique expands the potential therapeutic options for patients with relevant tricuspid valve regurgitation having a high risk for open heart surgery.

Keywords Tricuspid regurgitation • Transcatheter valve implantation • Percutaneous tricuspid valve replacement • Stent valve

Introduction

Tricuspid regurgitation (TR) is frequently encountered in patients with left heart valvular disease. With an increased volume of TR, cardiac output (CO) decreases and patients develop symptoms of right heart failure with congestive hepatosplenomegaly, peripheral oedema and ascites. Surgical repair or replacement, which is the only corrective therapy presently available, carries an operative

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mortality of up to 22% in this high-risk patient population.[1] Transcatheter therapy introduced to treat structural disease of the aortic, mitral, and pulmonary valves has expanded the therapeutic options for patients at high risk for conventional surgery.[2–5] However, for treatment of TR, no transcatheter technique is clinically available and only limited experimental data have been published so far.[6,7] In the present study, we evaluate heterotopic valve implantation in the central venous position for partial or full replacement of tricuspid valve function in an animal model of acute TR.

Methods

Description of device and delivery system

Self-expandable stents (28 and 26 mm in diameter, 50 mm in overall length) were manufactured of nitinol by laser cutting and equipped with radiopaque elements to facilitate visualization under fluoroscopy. Pulmonary valves harvested from porcine hearts were prepared as previously described and mounted to the stent by means of a 5-0 running suture.[8,9] To improve perivalvular sealing and decrease the risk of leakage, a pericardial sleeve (25 mm in length) was sutured around the outer surface of the stent. All devices were stored in 0.25% glutaraldehyde until use (*Figure 1*). For implantation, the stents were loaded into a flexible 21 F delivery catheter designed for the purpose of the study. The catheter allowed transvenous introduction over a central guide wire and afforded continuous flushing of the valve until deployment. Moreover, to ensure atraumatic implantation, the catheter tip is shaped as a cone and completely covers the stent to avoid endovascular lesions during the procedure.

Preparation of the animals

Thirteen female sheep (63 ± 6 kg) were included in the study. Studies were first performed as acute study with short-term observations (acute group, $n = 9$) to demonstrate feasibility and evaluate haemodynamics. After proof of concept, chronic studies with a 4-week follow-up period (chronic group; $n = 4$) were performed. All sheep were housed and fed according to the National Institutes of Health Guide for the Care and Use of Laboratory Animals federal guidelines (NIH Publication 85-23, revised 1985) and all procedures were approved by the local Ethics Committee. Animals were pre-medicated with 4 mg/kg intramuscular azaperon (Stresnil, Janssen, Neuss, Germany) and 0.02 mg/kg atropine (Braun, Melsungen, Germany). After induction of anaesthesia with intravenous administration of 5–10 mg/kg ketamine (Ketanest, Parke-Davis, Berlin, Germany) and maintaining with isoflurane 1–2%, animals were mechanically ventilated with 50% oxygen in room air using a volume-cycled ventilator (Siemens Servo 900C, Munich, Germany).

A standard central venous catheter and a 5 F PiCCO-catheter (Pulsion Medical Systems AG, Munich, Germany) were inserted in the left internal jugular vein and left femoral artery for continuous haemodynamic measurements, drug administration, and blood sampling (pH, oxygen tension, carbon dioxide tension, oxygen saturation, base excess, haematocrit, haemoglobin, glucose, and lactate; Radiometer ABL 520 Blood Gas Analyzer, Radiometer, Willich, Germany). The right internal jugular vein was surgically exposed and prepared with rubber vessel loops for introduction of the implantation catheter. After anticoagulation with 400 IU/kg heparin and 500 mg of acetylsalicylic acid, standard right heart catheterization was performed with a 5 F pigtail catheter from the right femoral vein to establish baseline haemodynamics [right ventricular pressure (RVP), right atrial pressure (RAP), inferior vena cava pressure (IVCP), arterial pressure (ABP), heart rate (HR), CO, arterial and central venous blood gases)]. Right ventricular and atrial angiography was initially performed to define the anatomy of the RV inflow tract. Cardiac output was measured by thermodilution technique using the PiCCO-System after injection of a bolus of 20 cm^3 cold saline into the central venous catheter. Three measurements were performed at each time

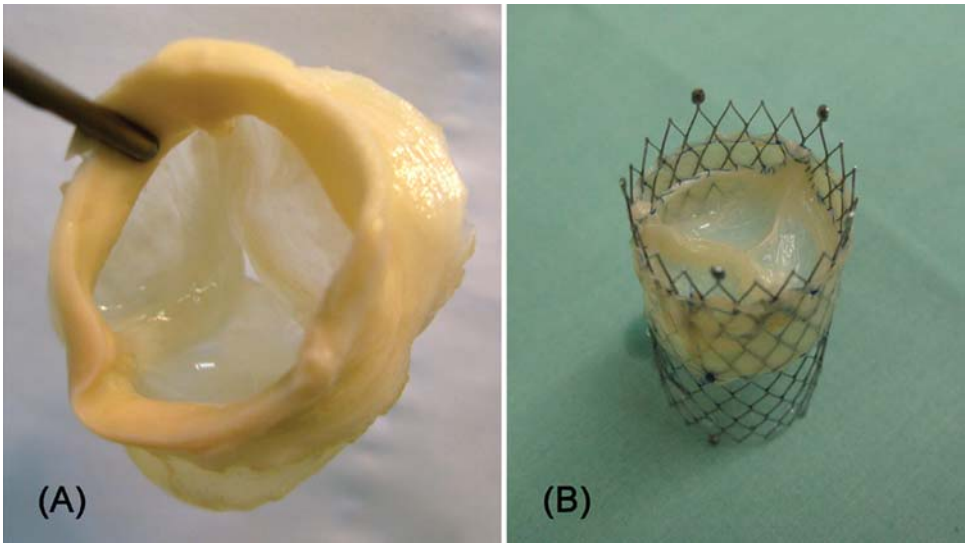


Figure 1 Self-expanding prosthetic valve. (*A*) Porcine pulmonary valve after pressure fixation in formalin and glutaraldehyde. Valves were carefully trimmed to remove excessive tissue and facilitate crimping into the delivery catheter. (*B*) Valves were then mounted to self-expanding nitinol stents of 28 or 26 mm in diameter. A pericardial sleeve was sutured around the outer surface of the stent to facilitate perivalvular sealing.

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point to increase reliability. All procedures were carried out under sterile conditions.

Creation of tricuspid insufficiency

Tricuspid insufficiency was created by use of a 0.07 inch wire blade designed for the purpose of this study. The blade was introduced under fluoroscopy through the right internal jugular vein into the RV and tricuspid chordae and leaflets were cut by repeated transvalvular pullback of the device. Severe TR was confirmed by ventricularization of right atrial and inferior vena cava (IVC) pressure recordings with an increase in mean pressure, and the presence of a prominent ventricular wave ('*v*'-wave) as well as by RV angiography.

Percutaneous implantation of the inferior and superior heterotopic valve

After creation of TR, a 5 F pigtail catheter (Medtronic, Minneapolis, MN, USA) was advanced from the right internal jugular vein across the right atrium into the IVC. Through this catheter, a 0.035 inch extra-stiff guidewire (Terumo, Tokyo, Japan) was positioned distally in the IVC. The image obtained by subsequent angiography of the IVC was subsequently used as reference on a second screen during valve deployment. The 28 mm valve was loaded into the implantation catheter and gently advanced over the central guide wire from the jugular vein in the IVC site. Under fluoroscopy, positioning elements of the stent were aligned approximately 20 mm below the IVC orifice and the valve was deployed by slow retraction of the outer sheath of the catheter (*Figure 2A* and *B*). After successful release of the IVC valve, the catheter was retracted from jugular vein and reloaded with the 26 mm valve for implantation in the superior vena cava (SVC). The device was advanced through the jugular vein into the SVC, the stent aligned approximately 20 mm above the SVC orifice and released as previously described (*Figure 2C* and *D*).

Haemodynamic measurements and evaluation of valve function

Haemodynamic parameters including RVP, RAP, IVCP, ABP, and CO were measured at baseline, after creation of TR, after implantation of each valve, and 1 h after the procedure. Pharmacological stress testing was performed in four acute animals by application of epinephrine to increase CO and blood flow through the valves.

Valve function was evaluated by angiography (acute group at the time of implantation, chronic group after implantation and after 4 weeks follow-up) and consisted of right atrial and ventricular angiography. At the time of sacrifice, thoracotomy was performed in both groups to allow for epicardial echocardiography. In all animals, an autopsy was performed to investigate the device position and inspect for macroscopic damage or thrombus formation. Valvular function and competency was roughly tested by passing fluid into the stent valves.

Statistics

All results are expressed as mean ± standard deviation (SD). Analysis of data was performed using a paired Student's *t*-test with two-sided comparisons, a *P*-value of <0.05 was considered to indicate statistical significance. Data analysis was performed using a statistical software package (SPSS for Windows, Version 15.0).

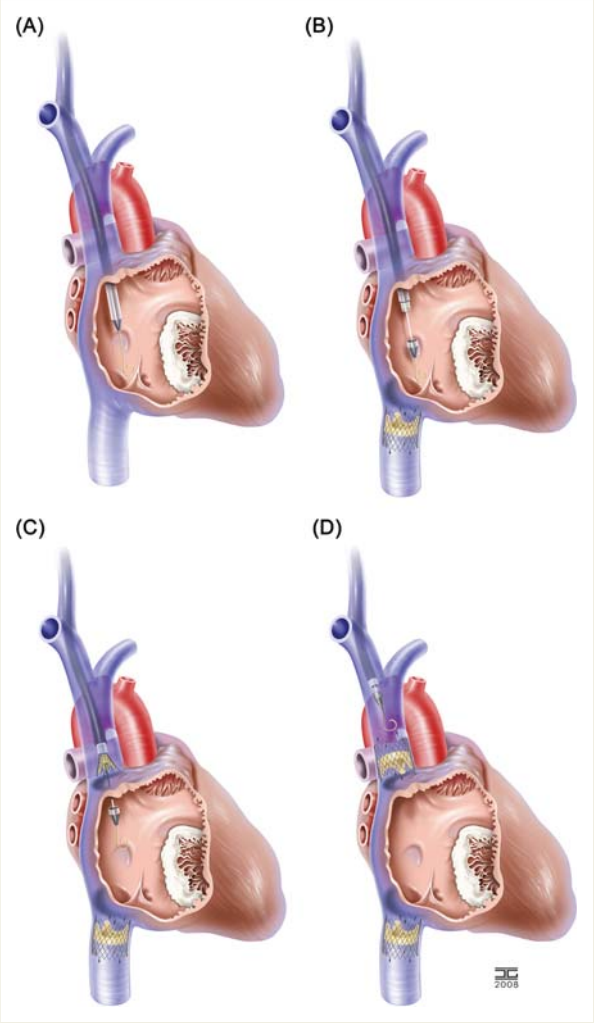


Figure 2 Concept and steps for heterotopic tricuspid valve implantation in the animal experiment. (*A*) advancement of the 21 F delivery system over a central guide wire into the inferior vena cava. (*B*) valve deployment in the inferior vena cava close to the right atrium approximately 20 mm below the inferior vena cava orifice. (*C*) Release of the valve in the superior vena cava approximately one inch above the orifice. (*D*) Position of both fully expanded valves after release.

Results

Acute group: measurements and proof of concept

Tricuspid regurgitation was successfully created in all animals and resulted in a prominent ventricular wave in the RA and the IVC with an increase in pressure from 10.1 ± 3.14 and 9.6 ± 3.47 mmHg to 16.2 ± 2.33 and 16.2 ± 2.82 mmHg, respectively. Cardiac output significantly decreased from 5.15 ± 1.69 to 2.9 ± 1.16 L/min. Valve implantation was then performed as described above (*Figure 3A–E*). Implantation of the IVC valve was successfully performed in all nine sheep in this group; however, implantation of the SVC valve failed in one sheep. In this animal, the device was

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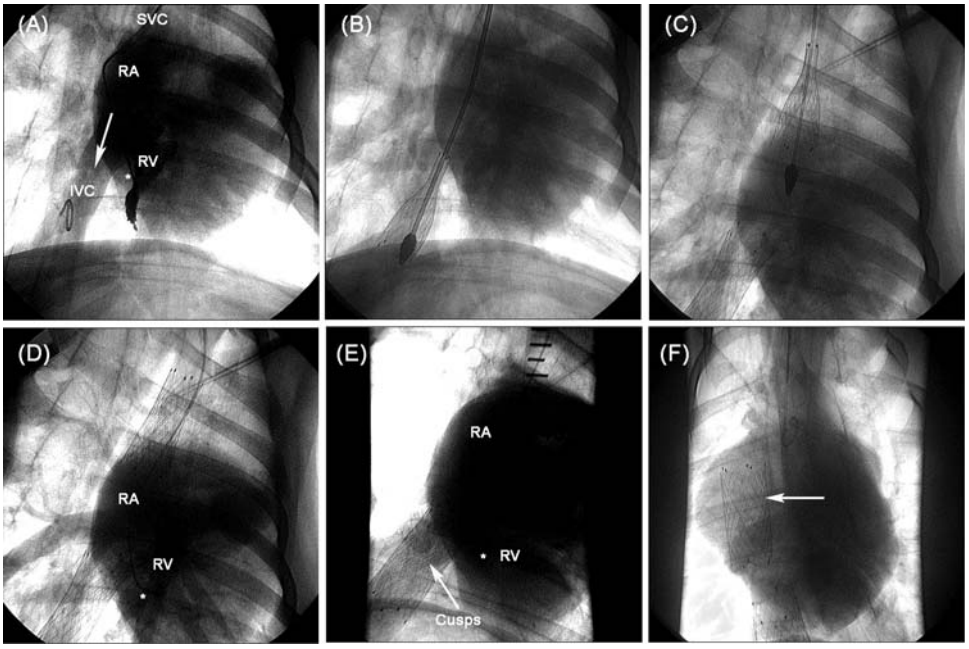


Figure 3 Implantation procedure. (*A*) Right ventricular angiogram demonstrating substantial tricuspid regurgitation with contrasting of right atrium and inferior vena cava (asterisk denotes the catheter used for right ventricular injection). (*B* and *C*) Stepwise implantation of valves into inferior vena cava and superior vena cava. (*D*) Right ventricular angiogram after valve implantation: the right ventricular and right atrium contrasts, no backflow in inferior vena cava and superior vena cava. (*E*) Cusps of the inferior vena cava valve are visible (arrow). (*F*) In one animal, implantation of the superior vena cava valve failed, the device embolized into the right atrium after release (arrow).

deployed too low in the SVC and migrated into the right atrium after release (*Figure 3F*). The animal developed atrial fibrillation with tachyarrhythmia and a decrease in blood pressure and haemodynamic instability, which, however, did not result in death of the animal.

After implantation of both devices, a significant reduction of the v-wave in the IVC was observed, whereas no major changes of right atrial and ventricular pressure were recorded. The 'y'-descent in the IVC decreased significantly compared with the corresponding atrial value (*Figure 4*). After implantation of both valves, CO increased to 4.2 $\pm$ 0.84 L/min. During the 1 h observational period, all haemodynamic parameters remained unchanged. Angiographic and echocardiographic evaluation including Doppler interrogation showed functioning valves in SVC and IVC positions (*Figures 3* and *5*). No severe valvular or paravalvular leakage was observed in any of the successfully delivered valves. During pharmacological stress testing, CO increased to 7.9 $\pm$ 1.30 L/min with an increase of right atrial v-wave to 21.0 $\pm$ 3.37 mmHg. Mean venous pressure in the IVC increased to 17 $\pm$ 4.24 mmHg. Haemodynamic parameters throughout the experiment are summarized in *Table 1*.

Macroscopic inspection during autopsy confirmed structural damage of the tricuspid valve, which affected both chordae and leaflets, along with isolated endocardial lesions of the RV caused by intraventricular manipulation. Appropriate valve position was verified in all cases except in one animal in which atrial migration of the SVC valve had occurred. In this animal, the sharp elements of the stent had perforated the atrial wall resulting in a haemopericardium. All other stent valves were very tightly positioned in the inferior and SVC, suggesting no paravalvular leakage macroscopically. No damage or perforation of the central veins or thrombus formation were observed in any of the animals (*Figure 6A* and *B*).

Chronic group: measurements and follow-up

In Group 2, TR was created in all animals and all devices were successfully implanted. When comparing acute and chronic animals, no significant differences in basic haemodynamic parameters were observed (*Table 2*). During follow-up, anticoagulation was afforded by daily administration of fractioned heparin and acetylsalicylic acid. The animals remained well during follow-up and did not develop clinical signs of cardiac failure. Animals were in sinus rhythm prior to implantation and remained so until the end of the study.

Evaluation at 4 weeks showed the devices in the desired position and demonstrated sealing in seven out of eight devices. No significant leak was observed by means of echocardiography and angiography in these valves. Autopsy showed that all devices were completely covered with fibrous tissue and adhered strongly to the vessel wall, making it impossible to retrieve the devices without causing structural damage (*Figure 6C* and *D*). No stent

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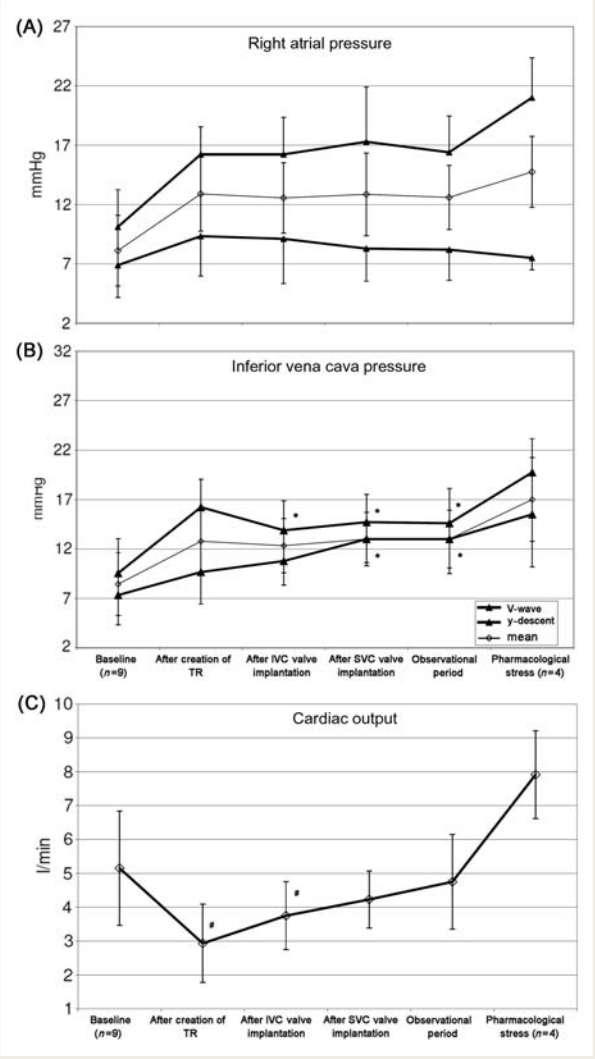


Figure 4 Time course of right atrial pressure, inferior vena cava pressure and cardiac output. Creation of tricuspid regurgitation results in increase in systolic and diastolic right atrial pressure (*A*) and inferior vena cava pressure (*B*). After Implantation of inferior vena cava valve, systolic inferior vena cava pressure decreases and diastolic inferior vena cava pressure increases. (*C*) Cardiac output is decreased with tricuspid regurgitation and recovers during valve implantation and observational period. *Significantly different from the corresponding right atrial pressure ($P < 0.05$); #significantly different from baseline value ($P < 0.05$).

fractures had occurred. Damage of leaflets and chordae of the tricuspid valve was confirmed in all animals.

In one animal, angiographic evaluation showed a significant paravalvular leak of the SVC valve. Autopsy confirmed partial migration of this valve approximately 20 mm from its original position towards the right atrium. Still positioned in the SVC, the distal part of the valve ended freely in the right atrium. This valve showed fibrous covering and strongly adhered to the venous wall as the other devices, thus suggesting early migration shortly after implantation.

Discussion

Transcatheter valve therapy is used in clinical practice for treatment of aortic, mitral, and pulmonary valve disease.[2–5] However, no interventional approach is yet available to treat TR. In the majority of patients, this condition is secondary to annulus dilatation resulting from increased pulmonary and RVPs in left heart disease. Progression of TR is associated with right heart failure with pulsatile venous hypertension, hepatic cirrhosis and peripheral oedema, which are often refractory to medical treatment. In this severely ill group of patients with frequent multiple comorbidities, surgical correction is associated with excessive mortality. Thus, a percutaneous approach would broaden the treatment options.

Boudjemline *et al.*[6] proposed and experimentally evaluated a catheter-based approach to TR by means of implanting a double-disc nitinol stent with a semilunar valve into the tricuspid annulus. Although technical feasibility was demonstrated in this animal experiment, several difficulties related to the orthotopic approach, including the problem of sufficient fixation of the self-expanding valve in the highly dynamic tricuspid annulus, were described and still remain unresolved. This experience was later confirmed by Bai *et al.*,[7] who also investigated percutaneous tricuspid valve replacement by orthotopic valve implantation in an animal feasibility study. The concept of orthotopic valve implantation based on currently available materials and techniques in human patients with RV and tricuspid annulus dilatation poses extreme challenges. In addition, experience involving percutaneous valve implantation in the tricuspid position in the setting of deteriorated bioprosthetic valves ('valve-in-valve' concept) or as treatment of TR in right-atrial to right-ventricular conduits in congenital heart disease has also been reported.[10,11]

In this experimental study, we investigated the concept of heterotopic tricuspid valve replacement via implantation of self-expanding valves into the inferior and SVC. Compared with orthotopic valve implantation, this approach has the advantage of avoiding the introduction of foreign material in the RV inflow tract and has a potentially lower risk of injury to ventricular structures, as valves are anchored in the large central veins away from the vulnerable endocardium. By reducing regurgitation of blood to the large central veins and thus venous congestion, this concept has the potential of alleviating the deleterious effects of TR.

In this experimental study in animals, we demonstrated feasibility of heterotopic valve implantation. All but one valves were correctly deployed as intended and no local complications were observed. In one acute animal, the upper valve migrated into the right atrium immediately after deployment as the device had been positioned too low in the SVC. This error can be avoided by careful angiographic or echocardiographic assessment of venous anatomy and with more experience with the technique. In one chronic animal, the SVC valve partially migrated towards the right atrium during follow-up, which resulted in paravalvular leakage. In contrast, all devices in the IVC remained in the desired position both in the early phase and during follow-up.

In all other animals, no complications associated with the implantation and function of the valves were observed in the

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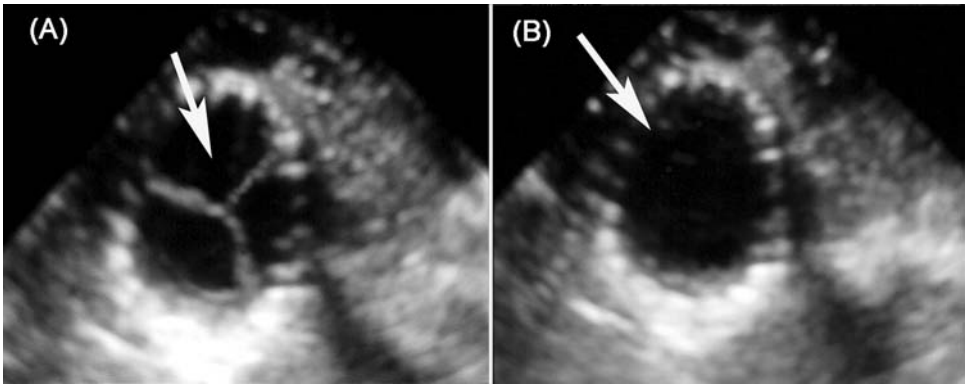


Figure 5 Echocardiographic evaluation of prosthetic valve function. Arrows demonstrate cusps of porcine pulmonary valve in inferior vena cava in (*A*) open and (*B*) close positions. The nitinol stent is visible surrounding the valve.

Table 1 Haemodynamic parameters throughout the experiment in the acute group

	Baseline	with TR	+IVC valve	+SVC valve	End of observation	Pharmacological stress ($n = 4$)
HR (b.p.m.)	78.7 (23.09)	105.3 (18.77)	96.0 (11.28)	105.3 (46.91)	85.0 (12.10)	158 (42.89)
RVP systolic (mmHg)	27.1 (7.82)	19.1 (4.19)	21.7 (4.47)	21.1 (5.77)	23.0 (5.67)	40.8 (3.78)
RVP diastolic (mmHg)	6.3 (3.54)	8.1 (3.04)	8.4 (3.24)	8.4 (3.21)	7.6 (2.30)	9.5 (2.08)
RVP mean (mmHg)	16.1 (5.00)	12.63 (2.50)	15.0 (5.39)	14.7 (2.43)	14.4 (2.07)	21.3 (2.22)
RA-V (mmHg)	10.1 (3.14)	16.2 (2.33)	16.2 (3.11)	17.3 (4.61)	16.4 (3.05)	21.0 (3.37)
RA-Y (mmHg)	6.9 (2.71)	9.3 (3.35)	9.1 (3.76)	8.3 (2.75)	8.2 (2.56)	7.5 (1.00)
RAP mean (mmHg)	8.1 (2.97)	12.9 (3.14)	12.6 (2.96)	12.9 (3.49)	12.6 (2.70)	14.7 (3.00)
IVC-V (mmHg)	9.6 (3.47)	16.2 (2.82)	13.9 (2.97)*	14.7 (2.81)*	14.6 (3.51)*	19.7 (3.40)
IVC-Y (mmHg)	7.3 (3.00)	9.7 (3.24)	10.8 (2.44)	11.4 (2.37)*	11.2 (3.49)*	15.5 (5.32)
IVCP mean (mmHg)	8.4 (3.17)	12.8 (3.19)	12.3 (2.74)	13.0 (2.71)	13.0 (2.91)	17.0 (4.24)
ABP systolic (mmHg)	119.6 (12.65)	56.3 (12.19)	69.6 (16.93)	64.1 (7.90)	82.0 (29.92)	186.7 (7.89)
ABP diastolic (mmHg)	86.2 (13.21)	38.8 (8.99)	47.8 (14.11)	40.1 (5.37)	56.6 (26.63)	129.5 (8.23)
ABP mean (mmHg)	90.0 (25.02)	47.2 (11.86)	56.5 (14.79)	49.1 (5.64)	66.6 (26.91)	148.0 (10.30)
CO (L/min)	5.15 (1.69)	2.9 (1.16)#	3.75 (1.0)#	4.2 (0.84)	4.75 (1.40)	7.9 (1.30)

Presented are mean (±SD) of nine sheep. HR, heart rate; RVP, right ventricular pressure; RA-V, right atrial *v*-wave; RA-Y, right atrial y-descent; RAP mean, right atrial mean pressure; IVC-V, inferior vena cava *v*-wave; IVC-Y, inferior vena cava y-descent; IVCP mean, inferior vena cava mean pressure; ABP, arterial blood pressure; CO, cardiac output.
*Significantly different from corresponding right atrial pressure ($P < 0.05$).
#Significantly different from baseline value ($P < 0.05$).

acute and chronic study. Catheter introduction, valve deployment, and fixation were straightforward. Moreover, no malfunction or stent fracture occurred. Chronic studies showed strong fixation of the valves to the venous wall by fibrous covering, making device migration beyond this period highly unlikely. The anticoagulation strategy proved sufficient in the experimental setting as no thrombo-embolic complications were observed in the study animals.

Study limitations and unresolved problems

In the present study, we demonstrated function and haemodynamic effects of heterotopic valves and evaluated acute and chronic results after heterotopic tricuspid valve implantation in an animal model of acute TR. In human patients, TR is usually secondary to annular dilatation resulting in substantially higher venous pressure. Thus, the animal model does not fully correspond to haemodynamic conditions and venous pressures present in patients with chronic TR. Further investigations, therefore, include the evaluation of long-term effects in secondary TR.

Transferring this concept to human patients requires consideration of the differences in vascular anatomy since the human IVC is shorter with the inflow of hepatic veins being closer to the right atrium. Employing a long stent with a pericardial sleeve here might lead to obstruction of the hepatic veins.

Although venous regurgitation is prevented by heterotopic valves, RV and atrial volume overload persist and may result

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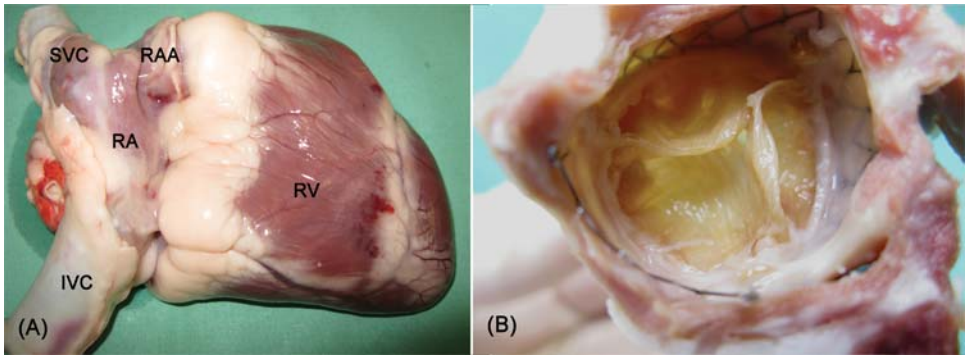


Figure 6 Macroscopic specimens. (*A*) Lateral view. Position of valved stents in the superior vena cava and inferior vena cava is visible (Group 1). RV, right ventricle; RA, right atrium; RAA, right atrial appendage. Macroscopic view (*B*) showing the inferior vena cava valve in chronic study (Group 2) after 4 weeks of follow-up. Note complete fibrous covering of the nitinol stent with strong adherence to the vessel wall, making retrieval impossible without structural damage.

Table 2 Haemodynamic parameters during implantation and after follow-up in the chronic group

	Baseline	with TR	After device implantation	End of chronic observation
HR (b.p.m.)	87.7 (5.51)	105.0 (12.15)	97.3 (13.63)	83.4 (17.10)
RA-V (mmHg)	9.8 (0.95)	14.8 (2.06)	15.3 (1.71)	15.0 (1.41)
RA-Y (mmHg)	6.5 (0.58)	8.8 (0.50)	7.9 (2.51)	9.5 (1.29)
RAP mean (mmHg)	8.0 (0.81)	12.9 (1.14)	11.7 (2.08)	11.5 (1.29)
IVC-V (mmHg)	10.0 (0.82)	14.9 (1.71)	12.7 (1.15)	12.0 (0.82)
IVC-Y (mmHg)	7.3 (0.95)	9.5 (0.58)	10.8 (1.53)	10.0 (1.41)
IVCP mean (mmHg)	9.0 (0.81)	12.25 (0.96)	11.7 (1.15)	10.8 (1.50)
CO (L/min)	5.8 (0.96)	4.1 (1.10)	5.4 (0.67)	5.2 (1.00)

Presented are mean (±SD) of four sheep. HR, heart rate; RA-V, right atrial *v*-wave; RA-Y, right atrial y-descent; RAP mean, right atrial mean pressure; IVC-V, inferior vena cava *v*-wave; IVC-Y, inferior vena cava y-descent; IVCP mean, inferior vena cava mean pressure; CO, cardiac output.

in potential deleterious effects on cardiac function and atrial rhythm during long-term follow-up. Valve implantation in the IVC and SVC results in ventricularization of the right atrium with persisting high atrial pressure and atrial dilatation, thus potentially promoting atrial fibrillation. However, the clinical implications and the potential deleterious effects during long-term follow-up of this approach are unkown and require further investigation. In fact, a single-valve implantation into the IVC might be sufficient to reduce venous congestion and improve patients clinical condition when applying this concept in humans.

In spite of the favourable results obtained in the present study and the proven feasibility, the study results also highlight the necessity for percutaneous devices to be specifically designed for application in the venous circulation. Current commercially available percutaneous devices are constructed for transcatheter aortic valve implantation in calcified aortic stenosis. Being either self- or balloon-expandable, these devices rely on fixation either in a rigid aortic anulus or in the ascending aorta as well as having to resist arterial pressure gradients. In contrast, the high venous wall elasticity and low pressure gradients prevailing in the venous system requires a specific stent design ensuring fixation as well as the use of tissue valves with optimal haemodynamic characteristics for application in the venous circulation.

In conclusion, this study demonstrates feasibility and offers new insights into percutaneous treatment of TR by heterotopic valve implantation in an animal model. The concept has the potential to broaden the therapeutic options in tricuspid valve disease.

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Conflict of interest: M.F. and H.R.F. are members of the scientific board of JenaValve Technology Inc., Delaware, USA.

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Publisher's note

The journal would like to clarify a statement made in an editorial entitled, 'The rise and fall of rosiglizazone, by Steve Nissen (EHJ, Vol. 31, Issue 7, page 773) which was inaccurate in the following sentence: 'the company subverted the editorial review process by stealing a copy of the manuscript'. The company did not steal the manuscript, but accepted, extensively used and distributed a confidential copy of it faxed by one of the reviewers assigned by the NEJM. This has been clarified now in the response by Prof. Steve Nissen (EHJ, Vol. 31, Issue 10, page 1284–1285). A response to the editorial has been published (EHJ, Vol. 31, Issue 10, page 1282–1284).