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CORRESPONDENCE

Research Correspondence

Heterotopic Valve Replacement as an Interventional Approach to Tricuspid Regurgitation

To the Editor: Tricuspid regurgitation (TR) is common in patients with late-stage myocardial and valvular heart disease. Severe TR leads to a decrease in cardiac output (CO), and significant symptoms of right heart failure develop, such as peripheral edema and congestive hepatosplenomegaly. Surgical correction with valve repair or replacement carries a high operative mortality risk and is therefore not routinely offered to many patients (1).

To date, no percutaneous approach to TR exists in clinical practice, and only limited experimental data have been reported (2,3). Boudjemline et al. (2) first described a catheter-based approach by implanting a double-disc self-expanding stent with a bovine jugular valve into the tricuspid annulus, and thus demonstrated the technical feasibility of this concept. However, several difficulties related to this orthotopic approach, including the problem of sufficient fixation of the valve in the highly dynamic tricuspid annulus, were observed. In human patients, in whom TR is often secondary to right heart dilation, this approach poses even further challenges.

The objective of our study was to evaluate the concept of heterotopic valve implantation in a central venous position for partial or full replacement of tricuspid valve function. We therefore designed a self-expandable heart valve manufactured with a tubular nitinol stent (diameter 26 and 28 mm) and mounted with a porcine pulmonary valve. The device was equipped with radiopaque elements to facilitate visualization under fluoroscopy. For implantation, the valves were loaded into a flexible 21-F delivery catheter designed for the purpose of this study (Fig. 1A). All procedures were approved by the local ethics committee.

Eight female sheep (64 ± 6 kg) were included in this study for concept investigation with the first-generation device. The animals were housed and fed according to the National Institutes of Health Guide for the Care and Use of Laboratory Animals federal guidelines (National Institutes of Health publication 85-23, revised 1985). After the start of anesthesia, right heart catheterization was performed with a 5-F pigtail catheter from the right femoral vein to establish baseline hemodynamics. Right ventricular (RV) and venous angiography was performed to define the anatomy of the superior vena cava (SVC) and inferior vena cava (IVC) and the RV. The CO was measured by a thermodilution technique with a PiCCO catheter (Pulsion Medical Systems AG, Munich, Germany) positioned in the left femoral artery. Three repetitive measurements were performed at each time point to increase reliability.

After surgical preparation of the right internal jugular vein, a 0.07-inch wire blade was introduced into the RV under fluoroscopy, and tricuspid chordae and leaflets were cut by repeated transvalvular pullback of the device. Severe TR was confirmed by the presence of a prominent ventricular wave in right atrial and IVC pressure recordings and by RV angiography. The implantation catheter was then advanced from the jugular vein over a central guidewire, and stepwise implantation of the IVC valve (28 mm) and the SVC valve (26 mm) was performed. Both devices were deployed approximately 20 mm from the atrial orifice of the IVC and SVC.

Hemodynamic parameters including IVC pressure, right atrial pressure, and CO were measured at baseline, after creation of TR, after implantation of each valve, and 1 h post-implantation. Valve function was evaluated by epicardial echocardiography and angiography. An autopsy was performed in all animals to investigate the device position and inspect for macroscopic damage or thrombus formation. Data analysis was performed using a statistical software package (SPSS for Windows, version 15.0, SPSS Inc., Chicago, Illinois). Comparisons were performed with the Student t test. Statistical differences were considered to be significant for values of $p < 0.05$.

In all animals, TR was successfully created and resulted in a significant decrease of CO from 5.1 ± 1.8 l/min to 3.0 ± 1.2 l/min. A prominent ventricular wave in the RA and the IVC was recorded with an increase of pressure from 8.4 ± 3.0 mm Hg and 8.3 ± 3.3 mm Hg to 16.0 ± 2.4 mm Hg and 15.8 ± 2.6 mm Hg, respectively. Device implantation was then performed as described previously. The IVC valve was successfully delivered in all sheep. In 1 animal, the SVC valve was deployed too low in the SVC and migrated into the right atrium after release.

After implantation of the IVC valve, a significant reduction of the ventricular wave in the IVC was observed (IVC ventricular wave 13.5 ± 2.9 mm Hg). After implantation of both valves, CO increased significantly to 4.4 ± 0.8 l/min. The y-descent in the IVC decreased significantly compared with the corresponding atrial value (IVC y-descent 11.0 ± 2.2 mm Hg vs. RA y-descent 7.7 ± 2.4 mm Hg). During the 1-h observation period, all hemodynamic parameters remained unchanged (at 1 h: CO 5.0 ± 1.4 mm Hg, IVC ventricular wave 14.0 ± 3.7 mm Hg, RA ventricular wave 15.5 ± 2.6 mm Hg).

Angiographic and echocardiographic evaluation showed functioning valves in SVC and IVC positions. No severe valvular or paravalvular leakage was observed in any of the successfully implanted valves. Macroscopic inspection at autopsy confirmed structural damage of the native tricuspid valve by rupture of chordae and leaflets. Appropriate valve position was verified in all cases. The stent valves were very tightly positioned in the IVC and SVC, suggesting no paravalvular leakage macroscopically (Figs. 1B and 1C). In 1 animal, atrial migration of the SVC valve had occurred, resulting in a hemopericardium caused by perforation of the atrial wall by sharp elements of the stent.

Multiple transcatheter approaches for valvular heart disease have been developed recently. However, no interventional technique is yet available to treat TR. A percutaneous approach to TR would broaden the therapeutic options and offer treatment in a severely ill group of patients with frequent multiple comorbidities. In this experimental study, we evaluate the concept of heterotopic tricuspid valve replacement via implantation of self-expanding valves into the IVC and SVC. The hemodynamic effects of the

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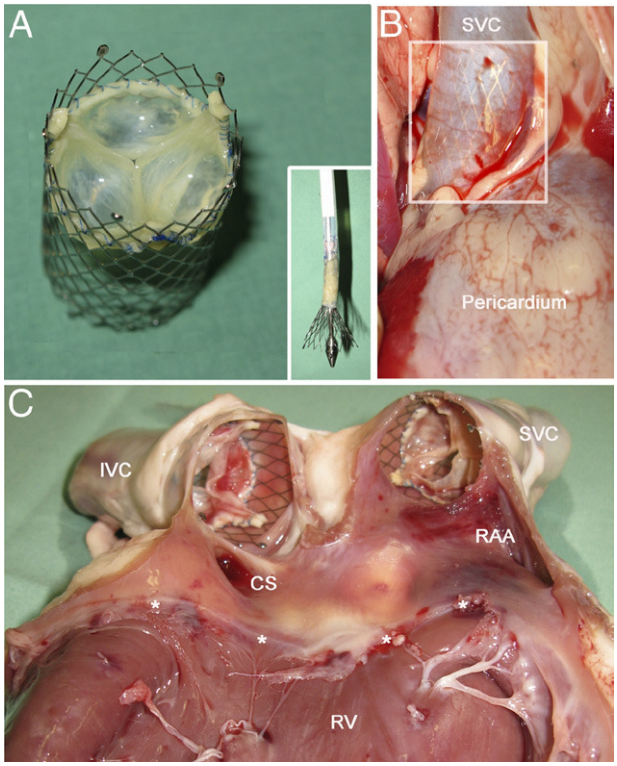

Figure 1 **Percutaneous Tricuspid Valve Replacement**

(A) Porcine pulmonary valves were mounted to self-expanding nitinol stents of 28 or 26 mm in diameter. The devices were implanted using a 21-F delivery catheter. **(B)** Macroscopic specimen showing the position of the valved stent in the superior vena cava (SVC) **(highlighted area)**. **(C)** Valve position in the SVC and inferior vena cava (IVC) after opening of the right atrium (RA) and right ventricular (RV) inflow tract. *Ruptured leaflets and chordae of tricuspid valve. CS = coronary sinus; RAA = right atrial appendage.

heterotopic valves were shown by an increase of CO and a decrease of venous regurgitation in an animal model of acute TR. Valve function was confirmed by echocardiography and angiography.

Compared with orthotopic valve implantation, this approach allows sufficient valve fixation and carries a potentially lower risk of injury to cardiac structures by avoiding the introduction of foreign material in the RV inflow tract. Except for 1 case of device migration, no further complications associated with the implantation and function of the valves were observed in this short-term study. Catheter introduction, valve deployment, and fixation were straightforward.

Several limitations exist and should be considered when applying this concept to human patients. First, TR in human patients is often secondary to annular dilation, with substantially higher venous pressures. Thus, this animal model of acute TR only partially represents the hemodynamic conditions in chronic TR. Second, anatomic differences should be considered because the human IVC is shorter than that in sheep, with inflow of hepatic veins close to the right atrium. These differences require further development of the device and will be surmountable with evolving technology. Third, heterotopic valve replacement reduces venous regurgitation; however, RV and atrial volume overload persist. The implications on cardiac and hepatic function and potential deleterious effects are unknown, and further studies are currently being performed to evaluate long-term follow-up. In conclusion, the concept of heterotopic valve implantation is feasible and has the potential to broaden the therapeutic options for patients with tricuspid valve disease.

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REFERENCES

1. Filsoufi F, Anyanwu AC, Salzberg SP, Frankel T, Cohn LH, Adams DH. Long-term outcomes of tricuspid valve replacement in the current era. Ann Thorac Surg 2005;80:845–50.
2. Boudjemline Y, Agnoletti G, Bonnet D, et al. Steps toward the percutaneous replacement of atrioventricular valves: an experimental study. J Am Coll Cardiol 2005;46:360–5.
3. Bai Y, Zong GJ, Wang HR, et al. An integrated pericardial valved stent special for percutaneous tricuspid implantation: an animal feasibility study. J Surg Res 2008 Nov 29 [E-pub ahead of print].

Letters to the Editor

Occurrence of Tako-Tsubo Cardiomyopathy and Chronobiological Variation

We read with great interest the paper by Citro et al. (1), in which the investigators found significant chronobiological variations in Tako-Tsubo cardiomyopathy (TTC) occurrence. In their large series, TTC was most frequently found in summer and in the morning.

We reviewed our cases of TTC from January 2000 to December 2008. We classified our patients (month, season, and time of symptom) according to the method of Citro et al. (1), and we surprisingly found differing results. In our series of patients (n = 51 [50 women], mean age 71 ± 11 years), the