Tricuspid valved stent implantation: novel stent with a self-expandable super-absorbent polymer

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Abstract

Objective: Trans-catheter aortic and pulmonary valve replacement procedures can result in favorable outcomes in selected patients. The aim of this study was to investigate the functioning of a novel self-expanding valved stent with super-absorbent polymer (SAP) for minimally invasive replacement of the tricuspid valve.

Methods: A newly designed nitinol stent with SAP was specially designed for the tricuspid annulus. This device was composed of right atrial anchoring elements, a left ventricular tubular stent, and a trileaflet bovine pericardial valve. The stent was coated with a waterproof material, and a pouch containing SAP for minimizing paravalvular leakage was placed beneath the atrial element. Seven pigs underwent minimally invasive off-pump tricuspid valved stent implantation. This was performed through a lower ministernotomy using a transventricular approach under transesophageal echocardiographic guidance. After 1 and 6 h, a complete echocardiographic evaluation and hemodynamics (Swan-Ganz catheter) were performed.

Results: Six of seven pigs exhibited normal hemodynamics immediately after tricuspid valved stent implantation and maintained stability for the entire period of monitoring. In one pig, a part of the atrial stent elements was deployed into the right ventricle, leading to significant paravalvular leakage, and died very soon. All subsequent animals survived with good results in the observation period. Accurate positioning of the valved stent was documented in six of seven pigs. SAP expanded and filled the gap between the stent and the native annulus in all animals. Mild paravalvular leakage was found in two of the six animals. Nevertheless, the observed leakage decreased to trace levels 6 h after implantation. In the additional four pigs, only trace tricuspid regurgitation was revealed. No right ventricular outflow tract obstruction was detected.

Conclusions: Trans-apical off-pump tricuspid valved stent implantation is feasible in an acute experimental setting, and SAP may help to reduce paravalvular leakages.

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1. Introduction

Trans-catheter aortic and pulmonary valve replacement procedures have already been performed in selected patients. This has prompted investigation into the feasibility of trans-catheter implantation of atrioventricular valved stents. Indeed, Boudjemline et al. reported that placement of a valved stent into the tricuspid position is feasible [1], while von Segesser et al. described trans-catheter mitral valved stent implantation at the same time [2]. When considering the use of such devices in patients with tricuspid regurgitation (TR), the gap between the native annulus and the stent presents an obstacle, especially because the tricuspid annulus is not exactly circular and because it must be dilated to various degrees in patients with severe TR [3]. Preservation of the tricuspid valve apparatus can be difficult due to the interference of the radial force of the stent and its positioning and rare repositioning. We recently reported successful trans-apical implantation of a new atrioventricular valved stent into the mitral position [4,5]. The goal of the present study was to investigate the utility of a novel valved stent with a self-expandable super-absorbent polymer (SAP), which practically diminishes the need to account for the gap between...
the native tricuspid annulus and the stent itself in a porcine
in vivo model using an off-pump technique.

2. Materials and methods

2.1. Device description

We designed a self-expanding valved stent constructed from a 0.55-mm nitinol wire. The stent consisted of three components: (1) an atrial element, (2) a tubular ventricular component, which comprised a nitinol self-expanding stent covered with a waterproof material, and (3) a ventricular fixation system, which was in a modified way already used in our trans-apical mitral valved stent implantation studies [4,5]. Atrial fixation system (a flat star-like disk), mild oversizing of the stent to exert small radial force on the native annulus, or, finally, a ventricular fixation system were used. This ventricular fixation system comprises four tethers of the ventricular column of the stent, which are fixed to the free ventricular wall close to the apex. The anchorage provided by the atrial elements in the right atrium (RA), the annular radial force, and the axial ventricular anchoring was strong enough to ensure stent security. The diameter of the atrial and ventricular components was 38 mm and 28 mm, respectively. The SAP was made of a cross-linked, acrylic acid polymer sodium salt (SANFRESH ST-573, Sanyo Chemical Industries Ltd., Kyoto, Japan). A doughnut-shaped pouch (outer diameter, 45 mm; inner diameter, 30 mm; and height, 7 mm) containing SAP (0.1 g) was deployed around the atrial component before stent implantation to be positioned above the tricuspid valve (Fig. 1(a) and (b)). After deployment, SAP absorbed aqueous fluids from the bloodstream. This results in gel formation and distension, which promotes sealing and reduces paravalvular leakage (Fig. 1(c)). The tubular ventricular component can accommodate a tricuspid glutaraldehyde-preserved porcine heart valve or a tricuspid bovine pericardial heart valve (diameter, 27 or 29 mm). The folded valved stent with SAP was 10 mm in diameter and 30 mm long. The valved stent was inserted with a custom-made delivery system through the apex of the heart. The delivery system consisted of a loading part with an external diameter of 12.5 mm and a total length of 28 cm, a cone-shaped catheter tip and grip part. The valved stent was folded using a crimper and was housed in the loading part. The outer sheath was pulled back by turning the grip, and the valved stent was held in place after confirming proper positioning using transesophageal echocardiography (TEE).

2.2. In vivo study preparations

Animals received humane care, according to protocols set forth by the Center for Experimental Animal Research at the University of Kiel, Kiel, Germany, in compliance with the Guide for the Care and Use of Laboratory Animal Resources, National Research Council, and published by the National Academy Press, revised 1996. Seven pigs (weighing 50—56 kg) were used in this study. A lower ministernotomy was performed under general anesthesia, continuous electrocardiography (ECG), and invasive blood pressure monitoring. A standard central

Fig. 1. (a) Top view, (b) lateral view before and (c) lateral view after implantation. Note: the expanded pouch made of super-absorbent polymer (SAP) after implantation (→).
venous catheter and a Swan-Ganz catheter were inserted in the left and right jugular veins, respectively, for drug administration and hemodynamic measurements. ECG, heart rate, mean blood pressure, cardiac output, right atrial pressure, right ventricular (RV) pressure, and pulmonary artery pressure were recorded before, 1 h, and 6 h after valve deployment.

2.3. In vivo studies

After a lower sternotomy was performed through a 5- to 6-cm skin incision, the pericardium was opened, a Favaloro retractor was placed, and the apex of the heart was exposed. Two rows of 3/0 polypropylene pledgeted felt purse-string sutures were placed around the RV apex. A heparin bolus (4000 units) was administrated intravenously. The valved stents were loaded into the delivery catheter, trans-apically inserted, and directly advanced into the right ventricle, using TEE for guidance. First, the atrial elements were partially deployed into the RA, and, then, the position of the delivery system was adjusted until the atrial elements of the partially deployed valved stent were exactly positioned above the tricuspid annulus. Afterwards, the remaining ventricular column of the valved stent was deployed by pulling back the outer sheath of the delivery system. After removing the delivery system, the tethers were partially pulled towards the right ventricle if needed. This helped to correctly position the stent. Finally, these tethers were secured to the RV wall as an axial ventricular fixation system.

Full TEE examination of the new valved stent was performed immediately after deployment, 1 h and 6 h after deployment.

2.4. Measurements

Data were collected for at least 60 min and up to 6 h after implantation to evaluate the hemodynamic stability and to assess the function of the new valved stent. TEE was initially performed before valved stent deployment to measure the maximum diameter of the tricuspid valve annulus, and was used during implantation to position the delivery system and to deploy the new valved stent across the tricuspid valve. TR and possible right ventricular outflow tract (RVOT) obstruction by the newly placed stent were assessed by color flow Doppler and pulse wave Doppler.

2.5. Statistics

All results are expressed as mean ± standard deviation (SD). The change over time of hemodynamic data was compared by Friedman’s chi-square r test followed by the Wilcoxon t-test with Bonferroni correction. A P-value of <0.05 was considered to indicate statistical significance.

3. Results

The preoperative data are given in Table 1 and the hemodynamic results are indicated in Table 2. The mean maximum diameter of the native tricuspid annulus was 31 mm (range, 29–33 mm). The mean time for surgical preparation of the apical access and the mean time for valved stent delivery was 38 min (range, 30–45 min) and 157 s (range, 90–180 s), respectively. Between one and four attempts were required to adequately position and deploy the valved stent across the tricuspid valve annulus. In pig 5, the atrial elements of the stent at the septal side were deployed into the right ventricle. In this pig, visualization by TEE was very difficult, so that additional attempts for correct positioning were necessary; this was achieved after four attempts. Six of seven devices were successfully deployed. In one pig, a part of the atrial element of the stent was deployed into the right ventricle. This incomplete deployment caused paravalvular leakage and a decrease in systemic blood pressure so that the pig was sacrificed. In this animal, the septal side of the atrial elements had migrated into the right ventricle. In all other animals, accurate positioning of the valved stent was established (Fig. 2 and Video 1). These animals exhibited normal hemodynamics after implantation of the tricuspid valved stent with SAP, with persistence of normal hemodynamics after 1 h. Non-sustained ventricular and atrial ectopic beats occurred during preparation of the apical access and during valve deployment in all animals. However, sustained or hemodynamically relevant arrhythmias did not occur during this study. Mild paravalvular leakage was found in two of the seven animals by TEE upon

Table 1. Summary of procedural data.

<table>
<thead>
<tr>
<th>Implant number</th>
<th>Weight (kg)</th>
<th>End-diastolic maximum diameter of the tricuspid annulus</th>
<th>Successful deployment of the stent</th>
<th>Number of attempts</th>
<th>Surgical access (min)</th>
<th>Stent implant (s)</th>
<th>Echocardiographic leak</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>52</td>
<td>31</td>
<td>No</td>
<td>1</td>
<td>45</td>
<td>150</td>
<td>Severe</td>
</tr>
<tr>
<td>2</td>
<td>56</td>
<td>30</td>
<td>Yes</td>
<td>1</td>
<td>43</td>
<td>120</td>
<td>Mild</td>
</tr>
<tr>
<td>3</td>
<td>55</td>
<td>32</td>
<td>Yes</td>
<td>1</td>
<td>40</td>
<td>180</td>
<td>Trace</td>
</tr>
<tr>
<td>4</td>
<td>54</td>
<td>33</td>
<td>Yes</td>
<td>1</td>
<td>35</td>
<td>250</td>
<td>Trace</td>
</tr>
<tr>
<td>5</td>
<td>51</td>
<td>32</td>
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<td>4</td>
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<td>100</td>
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<td>50</td>
<td>29</td>
<td>Yes</td>
<td>1</td>
<td>38</td>
<td>90</td>
<td>Mild</td>
</tr>
<tr>
<td>7</td>
<td>54</td>
<td>32</td>
<td>Yes</td>
<td>1</td>
<td>35</td>
<td>90</td>
<td>Trace</td>
</tr>
</tbody>
</table>

Table 2. Hemodynamic data before, 1 h and 6 h after valved stent deployment.

<table>
<thead>
<tr>
<th></th>
<th>Before</th>
<th>1 h after</th>
<th>6 h after</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (beats/min)</td>
<td>76 ± 7.4</td>
<td>86 ± 4.1</td>
<td>97 ± 9.7</td>
<td>NS</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>62 ± 4.5</td>
<td>62 ± 12.5</td>
<td>64 ± 4.9</td>
<td>NS</td>
</tr>
<tr>
<td>CVP mean (mmHg)</td>
<td>5.0 ± 0.9</td>
<td>6.2 ± 1.3</td>
<td>6.7 ± 1.4</td>
<td>NS</td>
</tr>
<tr>
<td>RVEDP (mmHg)</td>
<td>3.3 ± 1.0</td>
<td>2.8 ± 1.2</td>
<td>3.0 ± 0.9</td>
<td>NS</td>
</tr>
<tr>
<td>Transvalvular pressure (mmHg)</td>
<td>1.7 ± 1.2</td>
<td>3.3 ± 2.1</td>
<td>3.7 ± 1.0</td>
<td>NS</td>
</tr>
<tr>
<td>CO (l/min per m²)</td>
<td>3.4 ± 0.6</td>
<td>3.5 ± 1.3</td>
<td>3.7 ± 0.8</td>
<td>NS</td>
</tr>
</tbody>
</table>

HR, heart rate; MAP, mean arterial pressure; CVP, central vein pressure; RVEDP, right ventricular end-diastolic pressure; CO, cardiac output.
evaluation at 1 h after valve implantation (Tables 1 and 2). TR was expressed as an overall grade. Hence, with color jet extension, TR was classified into four grades: absent (0), trace or mild (1/4), mild-to-moderate (2/4), moderate-to-severe (3/4), and severe (4/4) [6].

However, paravalvular leakage decreased to trace levels by 6 h after implantation. Postmortem evaluation confirmed that the devices were correctly positioned in six of the seven animals. In those six animals, SAP had expanded and covered the gap between the atrial elements of the stent and the native annulus (Fig. 3).

4. Discussion

Conventional open-heart valve surgery is the gold standard for definitive surgical treatment of valvular disease, but this procedure may carry a high risk of complications in patients of advanced age and with significant co-morbidities. Trans-catheter valve surgery allowing for off-pump beating-heart valved stent implantation is a minimally invasive alternative to conventional heart valve surgery using cardiopulmonary bypass, and these procedures have already been conducted in selected patients with aortic and pulmonary disease and have gained increasing acceptance in high-risk patients.

TR often accompanies mitral or aortic valve disease and may regress gradually after left-sided valve surgery and correction of RV overload. However, in some patients, tricuspid valve insufficiency actually progresses and is often refractory to medical treatment. Because conventional surgical correction is associated with excessive mortality in these patients, a trans-catheter approach may be of particular benefit in this particular patient population.

A trans-catheter approach to treat TR is associated with several technical problems arising from the large size and irregular shape of the annulus, potentially resulting in complications with stent fixation and paravalvular leakage. However, Boudejemline et al. demonstrated the feasibility of orthotopic tricuspid valved placement by percutaneously implanting a double-disk nitinol stent with a semilunar valve into the tricuspid annulus in animals [2]. A similar report was published by Bai et al., who investigated percutaneous tricuspid valve replacement by orthotopic valved stent implantation in healthy animals with normal valves [7]. By contrast, Lauten et al. [8] advocated heterotopic tricuspid valve replacement via implantation of self-expanding valves into the inferior (IVC) and superior vena cava (SVC).

With a percutaneous orthotopic approach, the RV and tricuspid annulus dilatation cause difficulties in achieving sufficient anchoring and perfect sealing [2]. Moreover, the use of an oversized stent with sustained radial expansion force may result in myocardial trauma and disturbances in atrioventricular conduction. In a percutaneous heterotopic approach with implantation of the valved stent in SVC and IVC, although venous regurgitation is prevented by heterotopic valves, valve implantation in SVC and IVC may result in ventricularization with dysfunction of the RA with persisting RV and RA volume overload. This may, in turn, cause potential deleterious effects on cardiac function and atrial rhythm during long-term follow up [8].

The current study used a valved stent with an axial ventricular anchoring system and atrial element with SAP, without a ventricular edge or disk for fixation, thereby preserving the subvalvular tricuspid valve apparatus and avoiding myocardial injury or electrophysiologic compromise. To the best of our knowledge, this experimental study is the first to demonstrate the feasibility of implanting an orthotopic tricuspid valve stent prosthesis with SAP into the tricuspid annulus using a transventricular approach. We used a powdered, cross-linked, polymeric, acrylic acid sodium salt as the SAP. This study demonstrated the potential of SAP to eliminate the gaps between the native annulus and the stent and to minimize paravalvular leakage. Hydrogels such as SAP absorb aqueous solutions through hydrogen bonding with water molecules, to form a gel and become distended. We used this property of distension and the high flexibility of SAP to seal irregularly shaped gaps. It depends on the size of...
the pouch, which contains SAP. This polymer can absorb 300 times its weight in water. In this experiment, 0.1 g SAP was enough to distend the pouch to a 45-mm outer diameter, 30-mm inner diameter, and 7 mm height. Fortunately, in this acute study, we did not find any pulmonary embolisms. In our planned long-term studies, we will analyze possible problems with embolization and toxicity.

4.1. Complications

First, multiple preliminary in vitro and in vivo studies set the stage for the development of a suitable catheter delivery system and a valved stent, optimal handling of the device, an anchoring mechanism, and a suitable visualization method. Second, valved stent migration is frequently seen in experimental and human studies due to continuous cyclic movements of the heart. So far, stability of the valved stents can be achieved only by strong attachment to a calcified aortic or pulmonary annulus or through sustained radial expansion force of a valved stent to the surrounding tissue. The use of the radial force for anchoring the valved stent into the tricuspid position is prohibitive because of the ensuing obstruction of the adjacent RVOT.

5. Study limitations

This was a short-term study and does not describe the long-term durability of this technique and the novel, valved stent. Moreover, the trans-catheter tricuspid valved stent implantation was only performed in healthy pigs with normal heart valves. Another limitation of this study is the small number of pigs evaluated in this study. Toxicity and changes in the properties of the SAP during long-term follow-up also require further evaluation.

6. Conclusion

This study demonstrates the feasibility of transventricular beating-heart implantation of a valved stent with SAP into the native tricuspid valve in an acute setting.

Acknowledgments

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References


Appendix A. Conference discussion

Dr M. De Bonis (Milan, Italy): This very interesting study probably represents a further step towards the clinical application of transcatheter tricuspid valve replacement. Indeed, despite the small numbers of animals enrolled, the idea behind the development of this device and, in particular, the use of the super-absorbent polymer pouch, is certainly interesting and promising. However, as you acknowledged in the limitation section of your manuscript, the implantation was performed only in healthy pigs with normal heart valves. However, in the clinical setting of severe tricuspid regurgitation, the dilatation of the tricuspid annulus is very asymmetric, involving mainly the portions of the annulus corresponding to the anterior and posterior leaflets. And, of course, this may play a role in the incidence of paravalvular leaks. So I have three questions for you.

The first one is, in your initial experience was there a specific site where the mild leaks you reported were located? And do you think that modifying the shape of the atrial component of your device, in particular the pouch, could better fit the asymmetric tricuspid annular dilatation in order to decrease the incidence of paravalvular leaks?

My second question is, this pouch with super-absorbent polymer is going to be sitting in huge right atria and probably in patients with permanent atrial fibrillation. Do you think that this could significantly increase the risk of thromboembolic complications?

And, finally, do you believe that, in perspective, this type of valved stent will be suitable, after appropriate modification, for antegrade delivery through a fully percutaneous approach?

Dr Iino: For the third question, so far the stent with super-absorbent polymer is a little bit large for the percutaneous method. I think in the future we will be able to do this percutaneously, but so far we try to do it from the apex.

Dr De bonis: Have you ever thought about modifying the shape of the polymer pouch to fit the asymmetric dilatation of the annulus and where those leaks you reported were located. Were they more towards the anterior and posterior portion of the tricuspid annulus?

Dr Iino: I think the septal site.

Dr Lutter: On the septal site we have seen three of six, and in all the others we have also seen anterior and posterior leaflet sites with trace paravalvular leakages. You are right, it is elliptical or pear-shaped, so it is very difficult to put in a cylindrical valved stent. We are working on also having an elliptical valved stent, and this might further decrease these trace leaflet leakages we have observed after six hours.

Your second question was concerning any thrombosis onto these valved stents due to the polymer beneath the atrial element of the valved stent. These pigs were under IV heparin, and therefore we did not observe any thrombosis in them. But, you are right, in the patients we didn’t look for and we don’t know any long-term follow-up concerning thrombosis, and your concern is fully understood. The toxicity and other questions of durability of these valved stents will be analyzed in the future.

Appendix B. Supplementary data

Supplementary data associated with this article (Video 1) can be found, in the online version, at doi:10.1016/j.ejcts.2010.11.051.