Percutaneous valved stent implantation in the ascending aorta for the treatment of very high-risk aortic regurgitation: an animal study

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Abstract

Purpose: We investigated the effects of percutaneous valved stent implantation in the ascending aorta as an alternative treatment for aortic regurgitation in a canine model.

Materials and methods: A total of 16 healthy dogs weighing an average of 18.3 ± 2.1 kg were used for the establishment of animal models of chronic aortic regurgitation by percutaneous aortic valve perforation and balloon dilation. At 2 mo after successful model establishment, all experimental animals underwent valved stent implantation in the ascending aorta and then were followed up for 3 mo.

Results: Experimental models of chronic aortic regurgitation were successfully established in 10 dogs. Surviving dogs underwent successful valved stent implantation in the ascending aorta and were subsequently followed up for 3 mo. The level of instantaneous aortic regurgitation at 3-mo follow-up was significantly reduced compared with that before valved stent implantation (2.4 ± 0.9 versus 10.6 ± 2.1 mL/s, P < 0.05). The left ventricular ejection fraction was significantly increased (53.8 ± 4.2% versus 37.8 ± 3.7%, P < 0.05), and the left ventricular end-diastolic volume was also significantly reduced (30.3 ± 2.2 versus 40.1 ± 3.6 mL, P < 0.05). No paravalvular leak, stroke, atrioventricular block, or other complications occurred in dogs undergoing valved stent implantation.

Conclusions: Percutaneous valved stent implantation in the ascending aorta is feasible, effective, and safe as an alternative treatment for very high-risk aortic regurgitation in a canine model.

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1. Introduction

Aortic valve disease is the third most common cause of cardiovascular diseases, and the prevalence of degenerative aortic valve disease (DAVD) rises as life expectancy increases [1]. Most patients, however, with these diseases cannot tolerate traditional surgery because of physiological changes that occur with age and other comorbidities. We determined the risk of aortic regurgitation according to the factors such as clinical symptoms, the amount of aortic regurgitation, and left...
ventricular ejection fraction (LVEF) value. Severe aortic valve regurgitation showed by echocardiogram, LVEF of <40%, and recurrent left heart failure indicated very high risk. Because the first transcatheter aortic valve implantation (TAVI) was successfully performed, this novel technique has achieved rapid development [2]. Based on the encouraging results from some clinical trials, TAVI has become an alternative to surgical aortic valve replacement for the treatment of DAVD [3,4]. With continuous development of this technique, the traditional complications including vascular complications, paravalvular leaks, and coronary ostia involvement, still remain the leading cause of death, although their incidence has been significantly reduced.

We hypothesized that in the very high-risk patients with DAVD, implantation of a valved stent in the ascending aorta may avoid the blocking of coronary ostia and therefore theoretically decrease the mortality. It can also avoid the injury of calcified aortic valves and reduce the risk of paravalvular leaks and stroke. On the other hand, implantation of a valved stent above the coronary ostia will not affect the perimembranous conduction bundles, and this avoids the occurrence of atrioventricular block. Of course, implantation of a valved stent in the ascending aorta may affect the coronary blood flow because of nonphysiological position of the valve. In the present study, we established an animal model of chronic aortic regurgitation and performed percutaneous valved stent implantation in the ascending aorta. The experimental animals were followed up for a total of 3 mo.

2. Materials and methods

2.1. Valved stent construction

As previously reported [5–7], the valved stent was constructed using a conduit-shaped stent and an artificial valve. The artificial valve was constructed from a valve leaflet and valve ring. The valve ring was made of nitinol wire (Shanghai Malleable Alloy Company, Shanghai, China) with a radial diameter of 0.25 mm, bent into three crescent shapes. Porcine pericardium was used for valve leaflet creation after the removal of surface fat tissue, agitated digestion with 0.01% trypsin for 8 h, subsequent cross-linking with 0.6% glutaraldehyde for 36 h, and finally, repeated washing with 2% L-glutamine (to eliminate glutaraldehyde toxicity). The artificial valve was fixed inside the conduit-shaped stent, which was sutured with a 5–0 polypropylene thread. The valved stent was crimped by hand and then loaded into a 14F sheath (Fig. 1).

2.2. Animals

Sixteen healthy dogs (nine males and seven females), weighing an average of 18.3 ± 2.1 kg, were used. No abnormalities were found by preoperative electrocardiographic, thoracic radiographic, and color echocardiographic examinations. Animals were anaeasthetized initially by intramuscular injection of ketamine (10 mg/kg of body weight), followed by an intravenous injection of vecuronium bromide (2 mg). All animals were intubated and ventilated during the procedure. Propofol (0.1 mg/kg/min) was administered intravenously by a continuous rate infusion to maintain the anesthetic condition.

2.3. Ethics statement

All animals received care in compliance with the Guide for the Care and Use of Laboratory Animals published by the National Academies in 1988. The name of the Institutional Animal Care and Use Committee (IACUC) is Shanghai Hospital IACUC, and the ethics committee is Medical Ethics Committee of Shanghai Hospital. Both Shanghai Hospital IACUC and Medical Ethics Committee of Shanghai Hospital approved this study.

2.4. Establishment of a canine model of chronic aortic regurgitation

As previously reported [6], the canine model of mechanical acute aortic valve rupture was established. A small orifice was cut at the lateral edge of the pigtail catheter (Cordis, Johnson and Johnson, New Brunswick City, NJ) (Fig. 2), which was then advanced within the aortic sinus and pressed against the aortic valve leaflets under the guidance of ultrasound. A hard wire was advanced to the small orifice of the pigtail catheter to pierce the aortic valve leaflets; at the same time, balloon was inflated in the valve leaflet perforation. Angiography revealed obvious reflux through the valve leaflet perforation. Color Doppler echocardiogram was immediately used to evaluate the aortic valve regurgitation and LVEF. After the canine model of acute aortic valve rupture was established, the animals received postoperative intramuscular injections of penicillin (800,000 U). After 2 mo, all surviving dogs were
examined to evaluate the aortic valve regurgitation and LVEF with color Doppler echocardiography.

2.5. Valved stent implantation in the ascending aorta and postprocedural treatment

Valved stent was implanted in the ascending aorta as previously reported and shown in Figure 3 [6]. After valved stent implantation, all experimental dogs were bred 3 mo in an environment with a temperature of 15°C–25°C and humidity of 40% and were fed with feed and water three times a day. Postprocedural intramuscular penicillin and subcutaneous heparin (2500 IU/day) were injected for 3 d, and oral aspirin (3 mg/kg of body weight) was given for 30 d.

2.6. Follow-up at 3 mo after procedure

We assessed the eating activities, mental status, health status, living habits, and defecative activities of the dogs, especially the presence of dyspnea, oliguria, or abnormal behavior. At 3 mo after valved stent implantation, the electrocardiographic examination was repeated to detect potential arrhythmia, the trans-thoracic color Doppler was studied to quantify instantaneous aortic regurgitation, left ventricular volume, and ejection fraction, and the aortic angiography was performed above the valved stent to assess the stent location and its hemodynamic status.

2.7. Statistical analysis

All statistical analyses were performed using commercially available software (SPSS, version 15.0, for Windows; SPSS, Inc, Chicago, IL). A $P$ value of <0.05 was considered statistically significant. Normally distributed data are reported as mean ± standard deviation. Changes in instantaneous aortic regurgitation, LVEF, and left ventricular end-diastolic volume were compared using analysis of variance.

3. Results

3.1. Establishment of a canine model of chronic aortic regurgitation

Among the 16 experimental dogs, acute aortic valve rupture was not established in two dogs because the guidewire perforated the myocardium and led to cardiac tamponade, and the model of chronic aortic regurgitation was successfully
established in the other 14 dogs. On echocardiographic examination immediately after procedure, instantaneous aortic regurgitation was $5.3 \pm 0.6$ mL/s, LVEF was 62.4 $\pm$ 1.5%, and left ventricular end-diastolic volume was 26.2 $\pm$ 3.1 mL. Four dogs died of heart failure on days 20, 28, 35, and 41, and anatomic studies showed significantly enlarged ventricle, a lot of ascites, and hepatic congestion. All the other 10 dogs survived for 2 mo with significantly reduced exercise tolerance. Their weight was significantly reduced (16.4 $\pm$ 2.8 versus 18.3 $\pm$ 2.1 kg, P < 0.05).

Repeated echocardiographic examination showed that the level of instantaneous aortic regurgitation at 2-mo follow-up was increased significantly compared with that immediately after the procedure (10.6 $\pm$ 2.1 versus 5.3 $\pm$ 0.6 mL/s, P < 0.05). Significant mitral regurgitation occurred in four dogs. LVEF was significantly reduced (37.8 $\pm$ 3.7% versus 62.4 $\pm$ 1.5%, P < 0.05), and left ventricular end-diastolic volume was significantly increased (38.1 $\pm$ 4.2 versus 26.2 $\pm$ 3.1 mL, P < 0.05) compared with the postprocedural level (Table 1).

### 3.2. Immediate assessment after valved stent implantation

Valved stent implantation was successfully performed in 10 canine models. The procedure time was 37.4 $\pm$ 5.8 min, and the x-ray exposure time was 8.9 $\pm$ 1.4 min. Aortic angiography demonstrated that the prosthetic valve was located in the ascending aorta, without any prosthetic valve regurgitation and coronary ostia involvement. On echocardiographic examination, instantaneous aortic regurgitation was $4.4 \pm 0.8$ mL/s, LVEF was 38.5 $\pm$ 3.6%, and left ventricular end-diastolic volume was 39.2 $\pm$ 2.5 mL (Table 2).

### 3.3. Three-month follow-up after valved stent implantation

All dogs undergoing valved stent implantation survived for 3 mo, with increased body weight and improved exercise tolerance. No paralysis, abnormal behavior, abnormal living habits, hematochezia, or gross hematuria were observed. No stroke or other complications occurred in dogs undergoing valved stent implantation. Electrocardiographic examination showed no atrioventricular block occurred in any experimental dogs.

Aortic angiography demonstrated that the prosthetic valve had normal open and close function, and no valved stent was dislocated.

### 4. Discussion

The DAVD has been documented for more than one century but its etiology remains unclear. No etiologic treatment is available till now, and no effective way can be used to curb its development. TAVI is an effective treatment for high-risk elderly patients with DAVD who require surgical valve replacement. For those with very high risk, however, TAVI is still associated with a high mortality and various complications, which limited its clinical application [8,9].

In this study, animal models of chronic aortic regurgitation were established by a minimally invasive method, and the valved stent was percutaneously implanted in the ascending aorta. The procedural success rate achieved 100%. At 3-mo follow-up after valved stent implantation, the cardiac function of experimental animals was significantly improved, and no paravalvular leak, stroke, atrioventricular block, or other complications occurred. This novel method is expected to become an alternative treatment for very high-risk elderly patients with DAVD.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Normal</th>
<th>Acute AVR</th>
<th>Chronic AVR</th>
</tr>
</thead>
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<tr>
<td>N</td>
<td>16</td>
<td>14</td>
<td>10</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>18.3 $\pm$ 2.1</td>
<td>18.0 $\pm$ 1.2</td>
<td>16.4 $\pm$ 2.8$^1$</td>
</tr>
<tr>
<td>AVR (mL/s)</td>
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<td>5.3 $\pm$ 0.6</td>
<td>10.6 $\pm$ 2.1$^1$</td>
</tr>
<tr>
<td>LVEF (%)</td>
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<td>62.4 $\pm$ 1.5</td>
<td>37.8 $\pm$ 3.7$^2$</td>
</tr>
<tr>
<td>LVEDV (mL)</td>
<td>23.5 $\pm$ 2.7</td>
<td>26.2 $\pm$ 3.1</td>
<td>38.4 $\pm$ 4.2$^2$</td>
</tr>
</tbody>
</table>

AVR = aortic valve regurgitation; LVEDV = left ventricular end-diastolic volume.

$^1$ Compared with normal, P < 0.05.

$^2$ Compared with acute AVR, P < 0.05.

On echocardiographic examination, no paravalvular leak occurred. The level of instantaneous aortic regurgitation was significantly reduced compared with that before valved stent implantation ($2.4 \pm 0.9$ versus $10.6 \pm 2.1$ mL/s, P < 0.05). The LVEF was significantly increased (53.8 $\pm$ 4.2% versus 37.8 $\pm$ 3.7%, P < 0.05), and the left ventricular end-diastolic volume was also significantly reduced (30.3 $\pm$ 2.2 versus 40.1 $\pm$ 3.6 mL, P < 0.05) compared with that before valved stent implantation (Table 2).

### 4.1. Feasibility of canine model of chronic aortic regurgitation

The establishment of chronic aortic valve regurgitation in animal models through minimally invasive methods was a simple operation. In this study, the entire surgical procedure was completed within 30 min. The x-ray exposure time was relatively short. After 2 mo, the emergence of chronic aortic valve regurgitation, including left ventricular dilatation, reduced LVEF, mitral regurgitation, and increased aortic valve regurgitation, was fully in compliance with chronic aortic regurgitation pathologic features. In this experiment, relatively short time, rarely valvular destruction of surrounding structures, in this regard may not be very good simulation of human pathologic conditions, in vivo tissue calcification.

### 4.2. Feasibility of percutaneous valved stent implantation in the ascending aorta

The results of the present study indicate the simplicity of valved stent implantation in the ascending aorta. The valved stent designed for the experiment was braided with super elastic nickel–titanium alloy wires which have good compliance. Sewing the valve with a valve ring facilitated prosthetic valve construction. Additionally, the stent was connected with the valve ring, so that it was fixed precisely, and the valve ring was not easily dislocated. The pathway of valved stent implantation was similar to that of the occluder delivery for
the percutaneous treatment of congenital heart defect, which has been widely used in clinical practice. In the present study, all experimental animal models underwent successful implantation of valved stents, and the success rate achieved 100%. At 3-mo follow-up, no valved stent was dislocated. Therefore, we believe that the valved stent implantation in the ascending aorta is very feasible and safe.

4.3. Effectiveness of percutaneous valved stent implantation in the ascending aorta

In the present study, the echocardiography demonstrated significantly reduced aortic regurgitation, improved cardiac function, and narrowed left ventricle at 3 mo after valved stent implantation compared with those before the procedure. Valved stent implantation in the ascending aorta is helpful in reducing aortic regurgitation and improving cardiac function. Based on the straight tubular structure of ascending aorta, paravalvular leaks can be completely avoided using an appropriate valved stent with good wall apposition. Additionally, implantation of valved stent in the ascending aorta will not affect any native valvular or subvalvular structures and thus can avoid the occurrence of stroke or atriointerventricular block. During the 3-mo follow-up period after valved stent implantation, no paravalvular leaks, stroke, atriointerventricular block, or other complications occurred in our study. Therefore, we believe that the valved stent implantation in the ascending aorta can not only improve the cardiac function but also reduce the incidence of complications.

4.4. Disadvantages of percutaneous valved stent implantation in the ascending aorta

In fact, coronary blood supply and aortic valve function in patients with severe aortic regurgitation are not similar to those of normal population. Under a pathologic status, the mechanism of coronary blood supply may be very complex, and few previous studies focused on this issue. In our study, however, cardiac function significantly improved, and left ventricle significantly narrowed in the experimental animals at 3 mo after valved stent implantation in the ascending aorta, suggesting little adverse impact of valved stent implantation on coronary flow. If there was a significant adverse effect, the cardiac function of experimental animals might have further deteriorated.

4.5. Study limitations

First, current experimental animal models cannot imitate the high-risk aortic regurgitation completely. However, the main purpose of this study was to attempt to provide a simple and effective method to treat high-risk aortic regurgitation. Second, in this experiment, no further mechanism study was performed to evaluate the impact of valved stent implantation in the ascending aorta on the coronary flow. In the future, we will analyze the real situation of coronary flow and detail the short- and long-term impacts of valved stent implantation in the ascending aorta on the coronary flow.

Acknowledgment

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