Steps Toward Percutaneous Aortic Valve Replacement
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Background—To date, the surgical approach is the only option to replace the aortic valve. Percutaneous pulmonary valve replacement has recently opened new perspectives on transcatheter replacement of cardiac valves. We report our experience of aortic valve replacement through a percutaneous technique in lambs.

Methods and Results—A bovine jugular vein containing a valve was dissected and sutured into a stent. Twelve lambs were divided into 3 groups. In the first, a valved stent was implanted in the descending aorta after creation of an aortic insufficiency. In the second, the valve was implanted in the native position. In the third, we inserted a valved stent in the native position using an orientation mechanism. All valves were successfully delivered and functioned perfectly in short-term evaluation. All experiments in group 2 failed: 1 valve obstructed the coronary artery orifices, 1 stent was responsible for a major mitral valve insufficiency, and the third implant migrated prematurely. A paraprosthetic leak occurred in the last animal in this group. Animals in group 3 had successful implantation of the valved stent. The orientation mechanism allowed perfect alignment of the device without any damage to the coronary circulation or to mitral valve function.

Conclusions—Nonsurgical implantation of an aortic valve is possible in lambs in the descending aorta and in the native position. An orientation mechanism is obviously needed to avoid obstruction of the coronary orifices. With further improvements, this technique should be feasible in humans. (Circulation. 2002;105:775-778.)

Key Words: heart disease ▪ aorta ▪ valves

The treatment of stenotic valvular diseases consists of routine procedures in interventional cardiology.1–3 In particular, stenosis of mitral,4 aortic,5,6 or pulmonary valves7,8 can be treated by percutaneous dilatation with good results. However, surgery remains the first-line treatment for valvular insufficiency despite recent advances in pulmonary valve replacement via the percutaneous technique.9,10 We set out to develop a stent for aortic valve implantation that we aimed to test in the heterotopic and homotopic positions. We describe here our initial experience in a short-term animal study.

Methods

Device Preparation for Aortic Valve Replacement
A naturally valved venous segment harvested from the bovine jugular vein was mounted as described previously in a platinum-iridium stent (Numed Inc). Because of the position of the coronary arteries, this design did not permit implantation in the native position (Figure 1, left). Therefore, the venous wall was dissected and sutured with a 7.0 propylene thread along the commissures, which allowed space for the coronary orifices (Figure 1, right). The supporting structure of the leaflets was preserved to avoid structural insufficiency.

For a subgroup of animals, we designed and developed a modified stent with a deployment strategy in 2 steps. The first step was intended to ensure the orientation and locking of the device in the aortic orifice. The second step acted as a supporting structure for the heterograft. To guarantee precise orientation of this device with regard to the coronary orifices, we fixed an autoexpandable nitinol stent on a previously prepared valved stent (Figure 2). The nitinol stent had a spontaneous diameter of 25 mm. The branches congruous with the commissures of the implantable valve were sutured so that they were interdependent with the platinum stent wires and could not be deployed separately. Conversely, the branches congruous with the valve leaflets were not sutured to the platinum stent wires. Thus, when the platinum stent was reduced, the nonsutured branches of the nitinol stent were deployed, which defined a free space between the inner valved stent and the nitinol stent. This space was intended to shelter the native aortic leaflet at the time of implantation.

Preparation of Animals
Twelve lambs weighing 30 to 40 kg underwent catheterization for transcatheter implantation of a biological valve in the aortic position. Animals were equally divided into 3 groups with regard to the place of implantation in the aorta and the type of stent implant. In the first group, we examined the competence of the venous valve under aortic pressures. After creation of a massive aortic insufficiency, we intended to implant a valved stent in the descending aorta. The remaining 8 lambs underwent catheterization for percutaneous placement of a valve in the native position. In the second group, we intended to implant a valved stent without its orientation mechanism in 4 lambs. In the last group, we aimed to experiment with the stent with the 2-step deployment strategy. All animals were treated according to the European regulations for animal experimentation.11 Anesthesia was induced with 10 mg/kg thiopental and maintained with halothane in mechanically ventilated lambs. Cardiac and respiratory function were monitored throughout the procedure. The right
The carotid artery was prepared for catheterization. Heparin (100 UI/kg) was administrated twice during the procedure.

Creation of the Aortic Insufficiency
A Mullins sheath was first positioned in contact with one of the aortic leaflets. A transseptal needle was then inserted into the Mullins sheath so that the aortic leaflet was perforated. The sheath was subsequently advanced in the left ventricle through the hole in the leaflet. The transseptal needle was then retrieved, with the Mullins sheath left in the left ventricle. A guidewire was inserted into the sheath that was retrieved thereafter. An 18-mm balloon catheter was loaded on the guidewire, advanced, and inflated in the aortic valve. The inflation of the balloon tore the involved leaflet, which created an acute massive aortic valve insufficiency.

Aortic Valve Replacement and Deployment Strategy
The valved stent was crimped on the outer balloon of the delivery system (Figure 3). The stent was then covered by the plastic sheath of the delivery system and percutaneously inserted through the right carotid artery onto a previously positioned guidewire. In the first group, the device was advanced and deployed in the descending aorta as described previously for pulmonary implantation. In group 2, to avoid obstruction of the coronary ostia, the stent was deployed 1 cm below the aortic annulus. The external balloon was overdilated to fix the stent to the aortic wall. In group 3, the implantation technique was different (Figure 4). The valved stent was uncovered in the left ventricle, which deployed the nonsutured part of the nitinol stent. The system was thereafter pulled back in the area of the native aortic valve and pushed in the ventricle again. This push-and-pull technique was repeated until the free wires of the nitinol stent were positioned in the bottom of the native leaflets, with care taken to avoid pushing the stent inside the ventricle again. At this time, the balloons were inflated successively to deploy the valved stent to its final diameter. The balloons were deflated, and the delivery system was retrieved carefully, with the stent left in position. Thus, the native valve was trapped between the 2 stents and applied to the wall, which impinged its function.
Cardiac Catheterization and Testing of Implanted Valve Competence

Left ventricular and aortic pressures were measured at each step of the implantation. In the first group, left pressures were obtained before and after creation of the aortic insufficiency and after implantation in the descending aorta. Measurements were made below and above the implanted valve in the descending aorta, respectively, through a catheter inserted in the femoral artery and in the right carotid artery. In the remaining groups, pressures were measured on both sides of the implanted valve through the carotid artery. Angiographic evaluation consisted of aortography, left ventriculography, and selective coronary artery angiograms. Angiograms were performed before the procedure to define the anatomy of the aortic root and to measure the size of the annulus and/or the descending aorta. Studies were also repeated after implantation to confirm the appropriate position of the stent and to verify the function of the implanted valve.

Graft Retrieval

All grafts were explanted 1 hour after implantation. Before harvest, heparin (300 U/kg) was given intravenously. The aortic root was dissected carefully to accurately determine the position of the implanted valve with regard to the coronary ostia, native aortic valve, and mitral valve. All grafts were rinsed with a saline solution and inspected, and finally, valvular competence was tested ex vivo.

Results

In Vivo Testing of the New Device in the Descending Aorta

A massive aortic insufficiency was created in all lambs (Figure 5), and valves were then successfully implanted in the descending aorta. Mean size of the descending aorta was 20±2 mm. All implanted valves were 18-mm valves dilated at 18, 20, and 22 mm. Short-term evaluation showed perfectly competent valves. The valvular function of all retrieved grafts was perfect. Pressures in the descending aorta decreased from 115 (systolic) over 78 (diastolic) mm Hg (mean 95 mm Hg) to 108 (systolic) over 40 (diastolic) mm Hg (mean 55 mm Hg) after creation of the aortic insufficiency. After implantation of the valve, pressures in the descending aorta behind the valve were normal, which created a mean diastolic gradient at valve closure of 40 mm Hg.

Native Aortic Valve Replacement

The mean size of the aortic annulus was 23.25±1 mm. Despite the big annulus with regard to implant availability, we decided to perform the implantation to test the orientation mechanism and to assess the competence of overdilated grafts.

Lambs from group 2 died suddenly during the procedure despite successful (but inappropriate) delivery of the device.

Indeed, 1 valve obstructed the coronary artery orifices, which led to rapid ischemic arrhythmia. One stent encroaching on the left ventricle below the coronary arteries was responsible for a major mitral valve insufficiency. The third implant was deployed in precise position but migrated prematurely during angiography in the ascending aorta. The last valve impinged neither the function of the mitral valve or the coronary artery flow but was completely incompetent despite a dilatation diameter of 22 mm (Figure 6). At postmortem examination, the insufficiency was related to a paraprosthetic leak secondary to inappropriate placement of the stent.

Devices were successfully implanted in all lambs from group 3. The mean systolic transprosthetic gradient was 6±2 mm Hg. There was no stent migration in group 3. Angiographic evaluation revealed perfect position of all implants, with no mitral insufficiency and no coronary artery obstruction. The valve, with a diameter of 22 mm after dilatation, was competent angiographically and hemodynamically (Figure 7). The remaining 3 18-mm implanted valves were overdilated to respective diameters of 23, 24, and 25 mm. These were incompetent in various degrees ranging from mild to severe. At autopsy, the insufficiency was attributed to noncoaptation of the valve leaflets, which led to a central leak (Figure 8). As expected, the aortic native leaflets were trapped between the outer nitinol stent and the inner platinum stent, which totally inactivated this valve. Anterograde and retrograde catheterization of coronary arteries confirmed the nonobstructive position of the device. The commissures of the implanted valve were entirely aligned with the commissures of the native valve.

Discussion

We recently developed a valve that can be implanted by a percutaneous technique. The device is a biological valve harvested from mild to severe.
from the bovine jugular vein and mounted in a stent. It was initially developed for pulmonary valve replacement.

In vitro studies before human application showed that this valve could function in a simulated state of pulmonary hypertension (data not shown). These good results gave us the idea to enlarge the indications to the aortic valve. The close proximity of the coronary artery ostia to the aortic valve creates hurdles to percutaneous valve implantation. Moreover, the continuity between the aortic and mitral valves made the use of the initially designed device impossible. Therefore, we modified the stent to liberate a space for the coronary arteries. The venous wall was dissected along the commissures while attention was paid to leave the supporting valve tissue. Removal of the unnecessary tissue did not interfere with the function of the valve during in vitro testing. We then verified that this newly designed stent was competent in an acute in vivo test. Because in situ aortic valve replacement was unthinkable at this time, we successfully implanted the valved stent in the descending aorta in a group of lambs with traumatically created massive aortic insufficiency. Short-term evaluation with a mean diastolic transprosthetic gradient of 40 mm Hg showed perfect competence of all implanted valves. Moreover, 3 of 4 valves were dilated to a diameter that exceeded the original diameter without altering the function of the valve. This new valved stent design theoretically allowed for orthotopic valve replacement, but its precise placement was difficult. Indeed, the bad results from animals included in the second group highlighted the need for perfect orientation and anchoring of the device. Therefore, we developed a new implantation strategy based on a 2-step stent deployment. The first step ensured the orientation and hooking of the device in the desired position. The second step was the delivery of the valve itself. Thus, to achieve the orientation goal, we fixed a nitinol stent onto a valved stent. This material has the advantage of spontaneously recovering its form after crimping. To limit the form memory to the selected area, we sutured the wires congruous to the commissures. Thus, sutures along the commissures prevented deployment of these parts of the stent. Conversely, the wires in front of the valve leaflets were not fixed, which permitted self-expansion of these parts. This self-centering mechanism allowed alignment of the commissures of the native valve with the commissures of the valve to be implanted. This strategy was efficient in all tested lambs in short-term evaluation. The study was not designed for longer implantation, but such experiments are presently under way and are required before application in humans.

The risks of misplacement and embolization are maximal at the time of implantation. Questions regarding the orientation and hooking of the device have been answered by the present study. Long-term studies will address the question of the competence of the valve and its durability. Competence in the short-term study was good in 2 of 4 valves. The only valves available for the present study had a diameter of 18 mm. These valves were implanted despite an annulus larger than 22 mm to test the anchoring device. Therefore, regurgitation was related to lack of coaptation due to overdilation. Further studies with the use of bigger valves are presently under way in our laboratory. Bigger valves do not dramatically increase the size of the entire system, which makes percutaneous insertion possible in humans.

In conclusion, we report our steps toward aortic valve replacement using a percutaneous technique. Implantation into the descending aorta was necessary as a first step similar to early surgical experience by Hufnagel in the 1950s.12 As a second step, we approached the native valve position, confirming the major technical difficulties due to the anatomy of the site of implantation. Finally, we designed a self-centering system that allows precise placement of the valved stent by an anchoring mechanism. After further improvements, human application might be feasible. In particular, studies with longer follow-up are needed to appreciate the function and durability of bovine venous valve in systemic pressures. Further careful anatomic studies related to the implantation strategy must be performed on the pathological aortic valve in humans.

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References

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