

# Transcatheter Implantation of a Bovine Valve in Pulmonary Position

## A Lamb Study

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**Background**—Pulmonary regurgitation can lead to severe right ventricular dysfunction, which is a delicate postoperative problem in the long-term follow-up of patients who had surgery for congenital heart diseases. Clinical conditions of patients suffering from pulmonary valve incompetence are improved by valve replacement with a prosthetic valve. To date, the surgical approach is the only option to replace a pulmonary valve. We report the first experience of percutaneous pulmonary valve implantation.

**Methods and Results**—A fresh bovine jugular vein containing a native valve was sutured into a vascular stent and then cross-linked with a 0.6% glutaraldehyde solution for 36 hours. After being hand-crimped onto a balloon catheter, the device was inserted percutaneously according to standard stent-placing techniques. The valved stent was finally deployed in the position of the native pulmonary valve of the lamb. Hemodynamic evaluation was carried out before and 2 months after implantation. Anatomic evaluation was finally performed. Percutaneous pulmonary valve replacement was successful in 5 lambs. No complications were noted. Early and late angiographic and hemodynamic studies confirmed a good position of the stents with a competent valve at the end of the protocol. One stent was slightly stenotic, with macroscopically visible calcifications.

**Conclusions**—Nonsurgical implantation of pulmonary valves is possible in the lamb. This new technique is similar to standard stent implantation. Thus, it should be feasible in humans, in whom it will lead to a significant reduction of reoperations in patients in need of pulmonary valve replacement. (*Circulation*. 2000;102:813-816.)

**Key words:** stents ■ catheterization ■ prosthesis ■ valves

The pulmonary valve is generally considered to be the least important cardiac valve. However, in patients with congenital cardiac malformations who had surgical pulmonary valvectomy or transannular pulmonary patches, pulmonary insufficiency can lead to severe right ventricular failure.<sup>1,2</sup>

Surgical indications for pulmonary valve replacement in these patients are delicate. Cardiopulmonary bypass, in fact, aggravates right ventricular dysfunction, and clinical benefit for the patient solely through the reduction of the pulmonary regurgitant volume cannot be guaranteed.

We set out to develop a nonsurgical technique for placement of a biological valve in the pulmonary position through a percutaneous approach. Here, we report our initial experience of percutaneous pulmonary valve implantation in lambs.

### Methods

A vein segment containing a native biological valve was harvested from a bovine jugular vein, prepared, and sutured into a platinum stent. This unitary tubular structure was then reduced in profile and placed on a balloon catheter. The device was inserted percutaneously

according to standard stent placement techniques. The valved stent was finally deployed and fixed in the position of the native pulmonary valve of the lamb. Hemodynamic evaluation was carried out before and after deployment. The measurements were repeated 2 months after implantation, and anatomic evaluation was performed.

### Expandable Vascular Platinum Stent

The radially expandable vascular stent includes several cylindrical fine wire sections that are interconnected into a single tubular structure. The wires are made of a soft and highly malleable alloy consisting of ≈90% platinum and 10% iridium.

### Biological Valve

A jugular vein was harvested from a fresh bovine cadaver, and a section of the vein containing a native valve was selected for preparation. The valves were bicuspid or tricuspid, with extremely thin leaflets. Thereafter, the venous wall of the harvested section was trimmed to remove extraneous material and to reduce profile. However, sufficient material had to remain to allow safe attachment of the valved venous segment to the stent.

### Valved Stent

Before the biological valve was attached, the intravascular stent was preexpanded to a radial diameter of 18 mm. The biological valve was

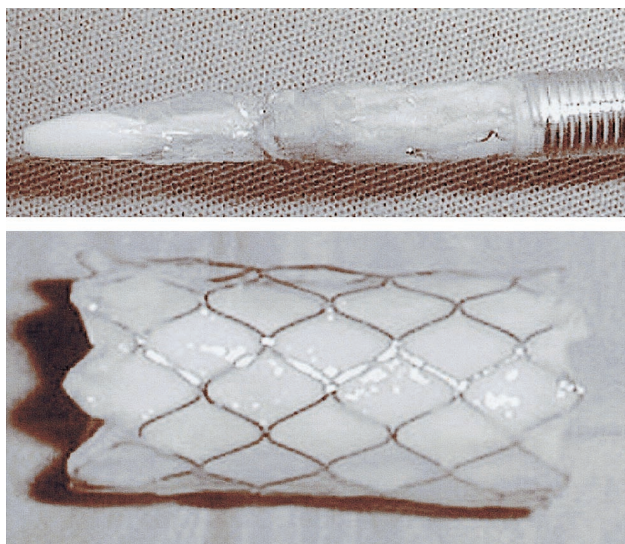
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**Figure 1.** View of valved venous segment in vascular platinum stent. Top, Stent reduced in profile and front-loaded into a 16F Mullins sheath.

then sutured to the interior of the stent with a 7-0 polypropylene thread. The tubular portion of the jugular vein spanned the entire axial length of the stent (Figure 1).

### In Vitro Testing

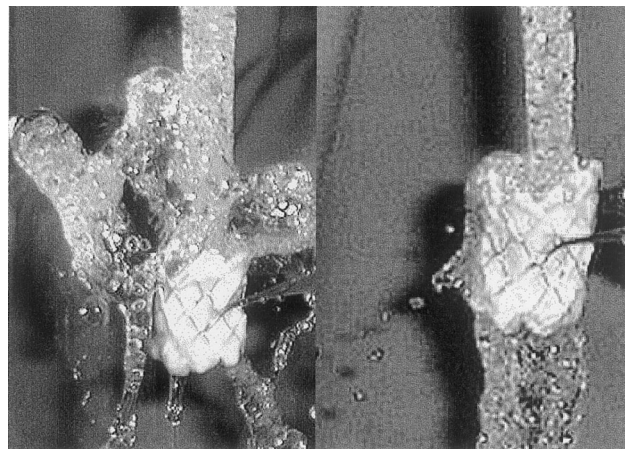
Fluid passing into the valved stent in the appropriate direction filled the pouch-like valvar sinuses defined by each of the leaflets. In this way, the valve leaflets coated inside the segment of the vein, thereby forming an effective valve closure. Fluid flow in the opposite direction was not restricted (Figure 2). The valvar competence was tested before and after crimping and reexpansion by the balloon catheter.

### Sterilization of Valved Stent

The valved stent was finally cross-linked with a buffered saline solution containing 0.6% glutaraldehyde for 36 hours at 4°C. After fixation, it was transferred to a 60% ethanol solution for storage. Before implantation, the valve assembly was immersed 3 times and carefully soaked in a physiological saline solution to remove the ethanol.

### Preparation of Animals

Eleven lambs 2 months old and weighing 16 to 18 kg underwent catheterization for transcatheter pulmonary valve replacement. All



**Figure 2.** Bench test of valved stent explanted after 2 months. Left, Effective closure of valve is demonstrated when stent is held under a stream of water. When stent is held in opposite direction, fluid is freely flowing, as seen on right.

lambs were treated according to the European regulations for animal experimentation.<sup>3</sup> Anesthesia was induced with 10 mg/kg of thiopental sodium and maintained with halothane in mechanically ventilated lambs. Cardiac and respiratory functions were monitored throughout the procedure. The right internal jugular vein was prepared for catheterization. Heparin (100 IU/kg) and penicillin were administered prophylactically. After the procedure, the jugular vein was preserved to allow for repeat catheterizations. Anticoagulant therapy was continued with low-molecular-weight heparin once a day and substituted 48 hours after stent implantation by low-dose aspirin.

### Implantation and Deployment Strategy

Through the internal jugular approach, a guidewire was positioned in the pulmonary artery. The valved stent was then hand-crimped onto the inflatable portion of an 18-, 20-, or 22-mm balloon catheter. The size of the balloon was dependent on the size of the pulmonary artery measured by angiography. To limit the risk of dislodgment or slipping of the balloon, the assembly was front-loaded in a 16F Mullins long sheath (Arrow), as shown in Figure 1. After the loading onto the previously positioned guidewire, the whole system was advanced and percutaneously implanted. The position of the valved stent was easily tracked fluoroscopically because of the highly radiopaque material of the stent. The valved stent was then balloon-expanded and deployed in the native pulmonary valve of the lamb to impinge upon the function of this native valve and to fix the device on the pulmonary wall. The balloon was subsequently deflated, and the catheter was removed, leaving the replacement valve assembly in the desired position.

### Cardiac Catheterization, Angiographic Studies, and Hemodynamic Evaluation

The right ventricular and pulmonary arterial pressures were measured before and after the implantation and before the animal was euthanized.

Angiography was performed before the procedure to locate the precise position of the native pulmonary valve, after the procedure to confirm the appropriate position of the stent and to verify the function of the implanted valve, and at the end of the protocol.

### Graft Retrieval

All grafts were explanted 2 months after implantation. Before harvesting, heparin (100 IU/kg IV) was administered. The valved stent was rinsed with a saline solution to remove excess intraluminal blood. All grafts were inspected macroscopically, and in vitro testing of valvar competence was repeated.

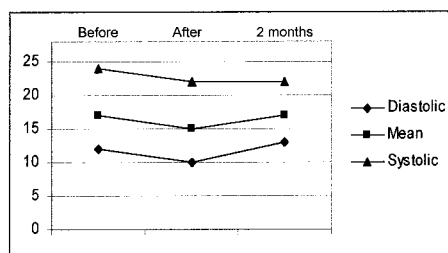
### Results

Seven of 11 lambs had implantation of a pulmonary valve. Technical failure occurred in the remaining 4 as a result of the narrow angle between the tricuspid valve and the right ventricular outlet.

In the 7 lambs that received implants, 5 stents were in the desired position, impinging on the function of the native valve of the lamb. In the remaining 2, the stent was implanted proximal to the valve in one and distal in the other.

No complications were noted during the procedure or the follow-up. There were no infectious processes. The mild fever that occurred in 2 animals disappeared within 48 hours without any antibiotic treatment other than the penicillin prophylaxis. No early or late migrations were observed.

The pulmonary systolic, diastolic, and mean pressures before and after implantation and before retrieval are shown in Figure 3. Six of the 7 valved stents were angiographically competent just after the procedure. The early evaluation of the seventh revealed a small insufficiency, probably due to the catheter in the pulmonary valve during the angiographic



**Figure 3.** Pulmonary pressures (mean in mm Hg) before and after implantation and after 2 months. Good function of valve is shown by unchanged diastolic pressures.

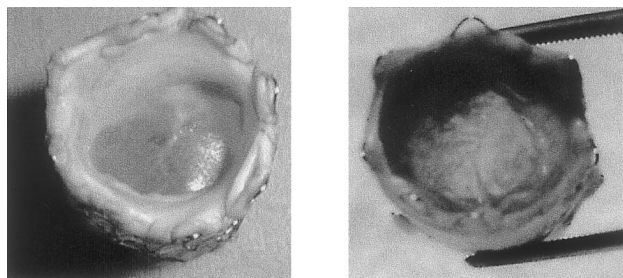
evaluation. One valved stent was mildly stenotic, with a 15 mm Hg pressure gradient between the right ventricle and the pulmonary artery.

In the 5 animals with a stent in the correct position, macroscopic findings at autopsy showed that the native pulmonary valve was nonfunctional because it was stuck between the pulmonary wall and the stent. The extremities of the stent were embedded into the pulmonary wall and the right ventricular outflow, respectively. Normal function of the native pulmonary valve was found in the animal with proximal placement of the stent. The valve inside the stent was completely covered by pannus ingrowth. The function of this valve could be restored *in vitro* after removal of the pannus. Similarly, the stent placed distal to the native valve interfered only partially with this valve. The valve in the stent showed one normally functioning leaflet, with the other being covered by pannus. The *in vitro* function of this valve could also be restored after removal of this fibrous tissue.

Among the 5 well-placed stents, 4 revealed transparent, mobile, and competent valves (Figure 4). One stent was slightly stenotic and showed macroscopically visible calcifications.

### Discussion

Pulmonary regurgitation can lead to severe right ventricular dysfunction, which is a delicate postoperative problem in patients who have undergone surgery for congenital heart disease.<sup>2</sup> Pulmonary insufficiency is usually well tolerated for a long time, but it overloads the right ventricle chronically.<sup>4</sup> Sometimes the conditions of patients with significant damage to the right ventricle can be substantially improved by pulmonary valve replacement.<sup>5</sup> Replacement is recommended in patients with deterioration of their clinical status or objective signs of right ventricular dysfunction. Furthermore,



**Figure 4.** Left, Valve before implantation; right, valve explanted after 2 months. Note thin and transparent leaflets.

in women who wish to become pregnant, valve replacement is advised even in the absence of symptoms.<sup>6</sup> To date, the surgical approach is the only option to replace a pulmonary valve to improve the clinical status and the actuarial survival rate of these patients.<sup>7</sup> Unfortunately, cardiopulmonary bypass may enhance right ventricular dysfunction, and clinical benefit from surgical pulmonary valvar replacement may therefore not be guaranteed.

Surgical pulmonary valve replacement is usually done with either homograft material from the human or the pulmonary valve from a pig.<sup>8</sup> In addition, the bovine pericardium has been widely used to construct pulmonary valves, and more recently, the native bovine jugular valve has been used as a valved conduit with very promising results.<sup>9</sup>

We had the idea of fixing a bovine jugular valve in an expandable stent designed for percutaneous placement. We sutured a valved venous segment into a stent. Thereafter, we verified the function of the resulting valved stent after reducing it in diameter and reexpanding it by a balloon catheter in our bench testing. The ability to reduce the external wall of the vein allowed us to reduce the diameter of the stent to a very low profile, without interfering with the function of the valve.

Recent improvements in interventional catheterization and stent technology have made percutaneous stent placement a routine procedure in pediatric as well as adult cardiology and radiology. More than 20 stent designs have been developed to fit the multiple indications.<sup>10</sup> Stents are used extensively in many cardiovascular applications, including stent placement in prosthetic conduits.<sup>11</sup> More recently, covered stents have enlarged the armamentarium of stent designs.<sup>12</sup> The outside layer on the covered stents led to a considerable increase in the diameter of these devices and to the use of big introducer sheaths. Therefore, experience with 16F introducers, as required for the placement of a valve on an 18- to 22-mm balloon, has already been acquired in other applications.

We succeeded in deploying 5 valved stents precisely in the native pulmonary valve of the lambs. In another 2 animals, stent delivery was possible, but the position of the stent was suboptimal, allowing for a residual function of the native pulmonary valve of the animal. In the remaining 4 lambs, we failed to implant the stent because of the narrow angle between the tricuspid valve and the right ventricular outflow. Unfortunately, the femoral vein of the lambs is of small size because of their small hind limbs. This forced us to use the jugular venous approach. However, the large size of the femoral vein in the human should allow for a straighter catheter course, which should reduce this technical difficulty.

The study was designed to continue for 2 months, considering the somatic growth of the lambs. In this period, all the lambs were completely asymptomatic and nearly doubled their body weight. At the end of the protocol, hemodynamic evaluation showed normal pulmonary pressure in all lambs in which stents were implanted. In the 5 lambs with correct position of the stent in particular, diastolic pressures in the pulmonary artery were as high as before implantation when the normal native valves were functioning. This confirmed the adequate diastolic valvar function throughout the time of the study. Moreover, only 1 animal had a mild systolic



pressure gradient of 15 mm Hg through the stent between the right ventricle and the pulmonary artery.

Pulmonary regurgitation occurred in 1 lamb, but angiographs were obtained with a catheter that passed through the valve. This made the interpretation of the pulmonary regurgitation difficult. After euthanasia, the *in vitro* testing confirmed a transparent, highly mobile, and well-functioning valve in 4 of the 5 lambs in which the stent position was accurate. The valve that was mildly stenotic showed macroscopic alterations with evidence of calcification. Interestingly, the 2 valved stents that were in suboptimal position had clear dysfunction of the valve. In 1, the function of the native valve of the lamb was entirely preserved, whereas the valve in the stent was embedded in fibrous tissue inside the stent. The stent, which only partially impeded the function of the native valve, showed 1 normally functioning leaflet, with the other being covered by the same fibrous reaction. After explantation, the valvar function of both stents could be restored for the bench testing by the simple removal of the fibrous tissue.

The degeneration of bioprosthetic valves has been widely studied in recent years.<sup>13</sup> Various etiological factors are involved that influence the durability of the valve to different degrees. The actuarial functional life of small valves (<25 mm) is shorter than that of larger ones. The role of ventricular systolic pressure in accelerating the degenerative process of bioprosthetic valves is also widely reported.<sup>14</sup> After 2 months of growth, our lambs essentially doubled their body weight. Therefore, the implanted stent inflated to 18 mm could have become stenotic, leading to an increased ventricular systolic pressure. Furthermore, the chemical treatment of the valves for sterilization obviously plays a major role in the durability of the valves and their tendency to calcify. The presence of degenerative processes and early calcification in 1 of the valves is likely to be due to the suboptimal sterilization process we used in our protocol.<sup>13,15</sup>

As far as degeneration of the valve is concerned, the inconvenience is the same between the surgical and the interventional approaches. The specific risks of the valved stent placement (dislodgment, balloon rupture, etc) are similar to the ones described in the literature for normal stent placement.<sup>16</sup> Therefore, they are likely to be very acceptable and less important than the damage from cardiopulmonary bypass associated with the risks of reintervention. A not fully expanded stent implanted in a child can potentially be redilated to adapt its size to the somatic growth without interfering with valvar function. We verified this with *in vitro* testing. Indeed, we expanded our valved stents to different sizes from 10 to 28 mm; the valves were completely competent and functioning well at all sizes. The use of bigger jugular veins allowed bigger diameters if needed. Moreover, in the lamb with the 15 mm Hg systolic pressure gradient between the right ventricle and the pulmonary artery, we dilated the stenosis effectively without interfering with the closure of the valve, as confirmed by the hemodynamic profile of the diastolic pressure.

Degenerated and stenotic valves in conduits, or better, in valved stents, potentially allow for a second valved stent implantation without the need for surgery. We explanted the

valved stent at the end of the study and showed that surgical stent removal is possible and therefore, surgical options are not hampered by even multiple stent implantations. The morbidity of reoperation might also decrease after improvement of the right ventricular function by preliminary valved stent implantation.

In conclusion, the future opportunity to implant pulmonary valves percutaneously in humans will lead to a significant reduction of reoperations in patients suffering from pulmonary valvar incompetence in need of a valve replacement. Although the implantation of such a valve is technically difficult in the lamb, application in humans should not fundamentally differ from routine stent implantation. The function of the implanted heterografts appears to be identical to bioprosthetic valves implanted surgically. Therefore, we think that percutaneous pulmonary valve implantation in humans should be possible in the very near future.

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