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Percutaneous Pulmonary Valve Replacement in a Large Right Ventricular Outflow Tract

An Experimental Study

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OBJECTIVES We report our initial experience with percutaneous pulmonary valve replacement in animals with large pulmonary trunks, using a modified percutaneous approach.

BACKGROUND Percutaneous pulmonary valve replacement has recently been introduced, and early clinical experience has been reported. This technique is presently limited to patients with a right ventricular outflow tract no bigger than 22 mm in diameter.

METHODS In seven animals (groups 1 and 3), we implanted a newly designed nitinol stent in the shape of a conduit with a central restriction of its diameter, containing an 18-mm bovine valve, as a one-step procedure. The animals in groups 1 and 3 were sacrificed after valve implantation and after two-month follow-up, respectively. In the second group (n = 3), we expected to percutaneously reduce the diameter of the pulmonary artery. Eight weeks later, we implanted an 18-mm valve mounted in a balloon-expandable stent. These animals were sacrificed after valve implantation.

RESULTS Eight of 10 devices were successfully delivered and were functioning perfectly at the initial evaluation and after two months. We failed to cross the tricuspid valve in two cases. The downsize mechanism allowed the pulmonary diameter to be reduced from 30 to 18 mm, without an impact on right ventricular function in any of the animals.

CONCLUSIONS Non-surgical implantation of a pulmonary valve is possible in ewes with all types of pulmonary trunk, regardless of its size. A "downsize" stent is needed to allow valve implantation in a large trunk. Further refinements will make this technique feasible in humans. (J Am Coll Cardiol 2004;43:1082–7) © 2004 by the American College of Cardiology Foundation

Until recently, surgery was the only technique available for cardiac valve replacement. Percutaneous valve implantation was first reported in animals and more recently in humans (1–6). The device we developed is a biologic valve harvested from the bovine jugular vein mounted in a balloon-expandable stent. However, because bovine jugular venous valves are available up to 22 mm in diameter, indications in humans are presently limited to patients who have a right ventricular outflow tract (RVOT) that does not exceed that

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maximum diameter. Unfortunately, the most common groups of patients requiring pulmonary valve replacement are children and adults who underwent transannular patch repair of tetralogy of Fallot (TOF) during infancy (7–9). Their pulmonary trunk is often larger in size. The biologic valves available at present do not reach this size, thus making percutaneous implantation technically unfeasible. Moreover, surgical valve implantation in such patients is usually associated with a size reduction of the RVOT and the introduction of a biologic valve or homograft. To broaden the indications of a percutaneous approach to the whole anatomic spectrum of pulmonary regurgitation, we developed a self-expandable stent that allowed us to downsize the diameter of the vessel to the available valve diameter. Because the deployment of such a stent could be hampered in a tortuous pulmonary anatomy, we also investigated a two-step approach in which valve implantation was delayed. We report our experience with these new stents in ewes that have a pulmonary trunk of at least 25 mm in diameter.

METHODS

Device preparation for downsizing the diameter of the pulmonary trunk. We designed and developed a self-expandable stent constructed from 0.27-mm nitinol wire in the shape of a conduit with a central restriction of its diameter (AMF, Groupe Lépine, Lyon, France). The overall length of the deployed device was 5.5 cm. The extremities had a spontaneous diameter of 30 mm, and the central restricted part had a diameter of 18 mm. The length of this

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Abbreviations and Acronyms

PA = pulmonary artery
PTFE = polytetrafluoroethylene
RV = right ventricular
RVOT = right ventricular outflow tract
TOF = tetralogy of Fallot

restriction was 15 mm, which is the approximate length of an 18-mm valve. To guarantee the perfect sealing of this device, we sutured a 0.3-mm polytetrafluoroethylene (PTFE) membrane, usually used for covered stent (Zeus Inc., Orangeburg, South Carolina), on the outside of the self-expandable nitinol stent with a 7.0-propylene thread (Fig. 1). This covered stent has been tested in vitro, with encouraging results (no stent fracture and no disruption of the PTFE membrane), but data showing long-term durability are presently missing.

For a subgroup of animals (one-step procedure), a naturally valved venous segment of 18 mm, harvested from the bovine jugular vein, was mounted into the restricted part of the self-expandable stent. The extremities of the downsizing stent were supposed to ensure the fixation of the device against the pulmonary wall. The central part of the stent ensured the downsizing of the pulmonary artery (PA) and

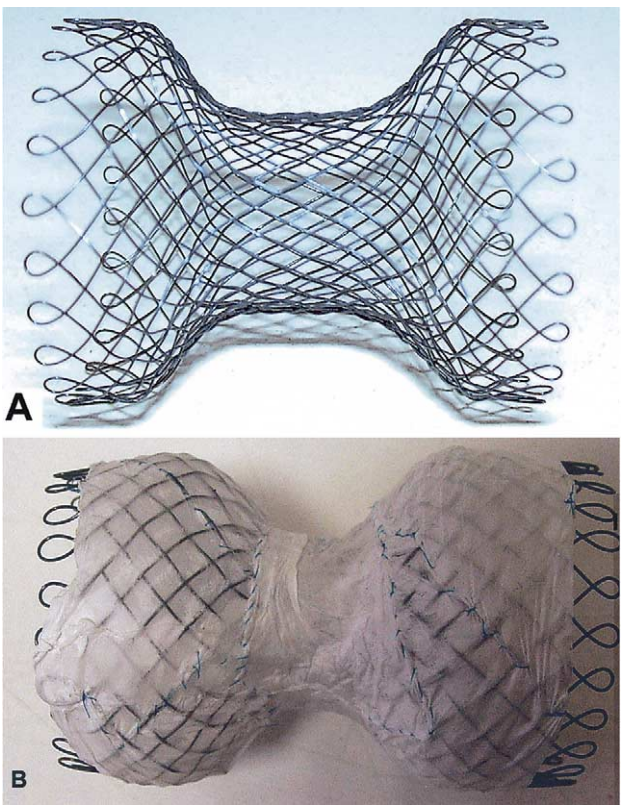

Figure 1. **(A)** The newly designed stent is shown uncovered. The extremities have a diameter of 30 mm, whereas the central part is 18 mm. **(B)** A polytetrafluoroethylene membrane is covering the stent to ensure sealing of the device.

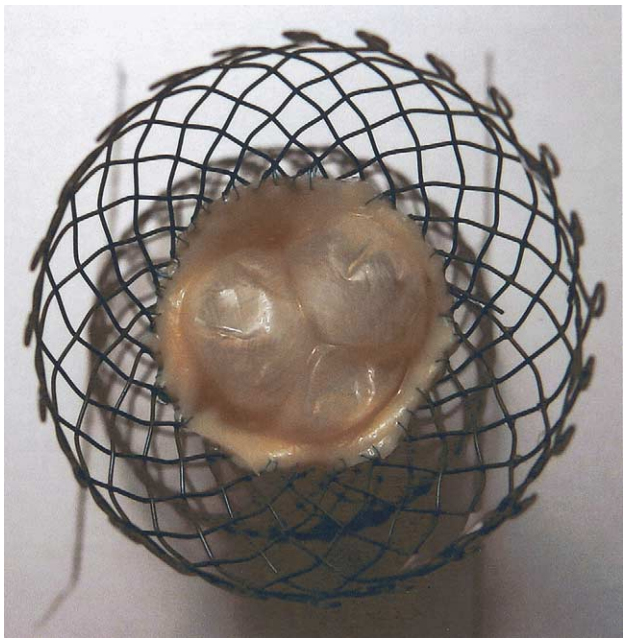

Figure 2. A front view of the stent, showing the valve in the closed position, as seen from the ventricular side.

acted as a supporting structure for the 18-mm heterograft (Fig. 2).

For the remaining group of animals (two-step procedure), the self-expandable stent was used non-valved to downsize the diameter of the vessel for a subsequent valve implantation with a Numed stent (Numed Inc., Hopkinton, New York). This latter device was prepared, as previously described, using an 18-mm valved segment sutured into a balloon-expandable CP stent (Numed Inc.) (1). All devices were stored in a glutaraldehyde solution.

Delivery systems. We developed a delivery system specifically for this application. It consisted of a front-loading long sheath pre-mounted with a balloon-in-balloon catheter inside, when used to deliver a balloon-expandable stent (Numed Inc.). A balloon was not necessary to deliver the nitinol stent. The distal part of the sheath is larger than the proximal part, liberating extra space for stent placement. Therefore, the outer size of the delivery system is 18-F distally when used to implant a valved stent (nitinol or CP stent) and 16-F when used to deliver the non-valved, downsizing nitinol stent. The length of this distal part was 7 cm for the self-expandable stent as compared with 5 cm for the balloon-expandable stent. The sheath can freely slide over the stent. At the tip of the catheter, a 1-cm-long dilator was glued to allow a smooth transition between the tip and the sheath, thus limiting the risk of traumatizing the vessel at skin insertion.

Repartition of animals. Ten ewes weighing 60 to 70 kg were included. Animals were divided into three groups according to the type of stent implanted and the length of time until sacrifice. In the first (n = 3) and third groups (n = 4), we intended to implant a 30-mm device sheltering an 18-mm valve as a one-step procedure. Animals from

groups 1 and 3 were sacrificed just after valve implantation and after two-month follow-up, respectively. In the second group (n = 3), we expected to percutaneously reduce the diameter of the PA to allow for further pulmonary valve placement. In this latter group, we intended to implant an 18-mm valve into the previously placed stent 6 to 10 weeks after the first procedure. Animals from this group were sacrificed just after valve implantation.

Percutaneous reduction of pulmonary trunk diameter and pulmonary valve replacement. All ewes underwent catheterization for transcatheter implantation of a biologic valve in the pulmonary position under general anesthesia. Anesthesia was induced with 10 mg/kg of thiopental and maintained with halothane in mechanically ventilated ewes. Cardiac and respiratory functions were monitored throughout the procedure. The right jugular vein was prepared for catheterization. Heparin (100 IU/kg) was administrated once during the procedure. Animals from group 3 received a low dose of aspirin and intramuscular low-molecular-weight heparin twice daily throughout the two-month follow-up. All animals were treated according to the European regulations for animal experimentation (10).

In groups 1 and 3, the valved device was loaded into the 18F delivery system (Numed Inc.) and inserted through the right jugular vein over a previously positioned 0.035-inch (0.089-cm), extra-stiff guide wire (Amplatzer, Golden Valley, Minnesota). The device was advanced and deployed in the pulmonary trunk by simply uncovering the device. By applying the native valve to the wall of the vessel, the stent impinged on the native valvular function. A balloon was not needed for deployment of this device.

In the second group, we aimed to test a stepwise implantation. Using the same technique, a non-valved device was implanted using a 16-F delivery system. In our experience in ewes, pulmonary regurgitation created by the implantation of a non-valved stent frequently led to severe growth impairments and/or animal death (unpublished data). Moreover, because we aimed to test the feasibility of a two-step procedure, failure of the native valve was not mandatory to answer that question. Therefore, the tested non-valved device was implanted above the native pulmonary valve, which remained functional. Six to 10 weeks later, the animals were recatheterized to implant a biologic valve. A 0.035-inch, extra-stiff wire (Amplatzer) was positioned in the distal right PA through the previously placed stent. After rinsing, the valved stent was crimped down on the outer balloon of the 18-F delivery system and covered before its skin insertion, as previously described (1). The delivery system was loaded onto the guide wire and advanced into the restricted part of the previously placed stent. The valved stent was then uncovered and deployed within the restricted part of the previously placed stent by subsequently inflating the inner and outer balloons of the delivery system. The balloons were finally deflated and retrieved with the delivery system, leaving the valved stent in the deployed position. The valved stent was dilated to match the diameter of the restricted part of the first stent to the diameter of the available valves (18 mm). Because the RVOT was larger than 18 mm, the restricted part of the nitinol stent was mandatory to secure the 18-mm valve supported by the balloon-expandable stent.

Cardiac catheterization and testing of implanted device. Right ventricular (RV) and pulmonary pressures were measured before and after device implantation to determine the gradient across the stent. Angiographic evaluation consisted of a pulmonary injection distal to the device and right ventriculography. Angiograms were obtained before the procedure to define the anatomy of the pulmonary root and to measure the size of the pulmonary trunk. Studies were also repeated after implantation and before the animals were sacrificed to confirm the appropriate position and sealing of the stent, as well as to verify the function of the implanted valve.

Graft retrieval. Grafts were explanted just after valve insertion in animals from groups 1 and 2 (immediately in ewes from group 1 and 2 months after the initial procedure in animals from group 2) and two months after valve implantation in animals from group 3. Before harvesting, heparin (300 IU/kg) was intravenously given. The heart and lungs were retrieved together in one block. The pulmonary vascular tree was examined to determine the position of the implanted device in relation to the pulmonary valve annulus. The device was then harvested with a section of the PA and rinsed to remove excess intraluminal blood. All grafts were inspected, and the competence of the valve was grossly tested by passing a fluid over the graft. All lungs were dissected and inspected macroscopically to look for lung infarcts.

RESULTS

One-step pulmonary valve replacement (groups 1 and 3). The mean size of the pulmonary trunk was 26 mm. Six of seven devices were successfully implanted. In one animal, it was impossible to cross the tricuspid valve. The mean systolic transprosthetic gradient was 11 mm Hg (range 8 to 16 mm Hg) (Table 1). This gradient did not significantly change when comparing short- and long-term evaluations (11 vs. 11.25 mm Hg). There was no early or late stent migration. Angiographic evaluation revealed that the implants were in the desired position and confirmed the sealing of the stent cover, with no leak between the device and pulmonary wall. Valves were competent angiographically and hemodynamically (Fig. 3). No stent fracture was observed. At autopsy, valve leaflets were thin and perfectly mobile in the early as well as late implantations. In group 1, coagulated blood was trapped between the restricted part of the stent and the vascular wall, so there was an absence of blood flow in this area. In group 3, where animals were harvested two months after implantation, all devices were fixed to the pulmonary wall, and nitinol wires were partially covered by fibrous tissue (Fig. 4). No macroscopic lung

Table 1. Hemodynamic Data

		Timing		
	Mean Pressures (mm Hg)	**Before Implantation**	**Just After Implantation**	**After 2-Month Follow-Up**
Groups 1 and 3	RVP (S/D/ED)	22/0/6	35/0/8	36/0/6
	PAP (S/D)	22/12	24/13	25/14
Group 2	RVP (S/D/ED)	25/0/8	33/0/8	NA
	PAP (S/D)	23/10	24/12	

D = diastolic; ED = end-diastolic; NA = not applicable; PAP = pulmonary artery pressure; RVP = right ventricular pressure; S = systolic.

infarcts were found. However, no histologic study was made to eliminate small lesions. No macroscopic vascular damage was noted when inspecting the vascular wall along the device. As expected, the pulmonary native leaflets were applied between the stent and the pulmonary wall, thus totally inactivating them.

Two-step pulmonary valve replacement (group 2). The mean size of the pulmonary trunk was 26.3 mm. A diameter reduction of the pulmonary trunk was possible in all animals. The mean systolic transprosthetic gradient was 9 mm Hg (range 5 to 12 mm Hg). The RV/aortic pressure ratio was <50% in all animals. Angiographic evaluation confirmed the perfect position of all implants, without any leak between the device and pulmonary wall (Fig. 5). All ewes survived the first procedure, but two of three ewes successfully received the valvular implant two months later. In the remaining animal, despite several attempts, we failed to cross the tricuspid valve. Indeed, coming from the jugular vein, the angle between the tricuspid valve and RV outlet was too narrow to allow for advancement of the device in the desired position. The competency of the implanted valves was confirmed at angiographic evaluation and autopsy. There was no evidence of stent fracture. The valved stent was in a good position within the restricted part of the nitinol stent. The external stent was fixed to the PA wall. As expected, the native pulmonary valve was not damaged and thus functioned normally.

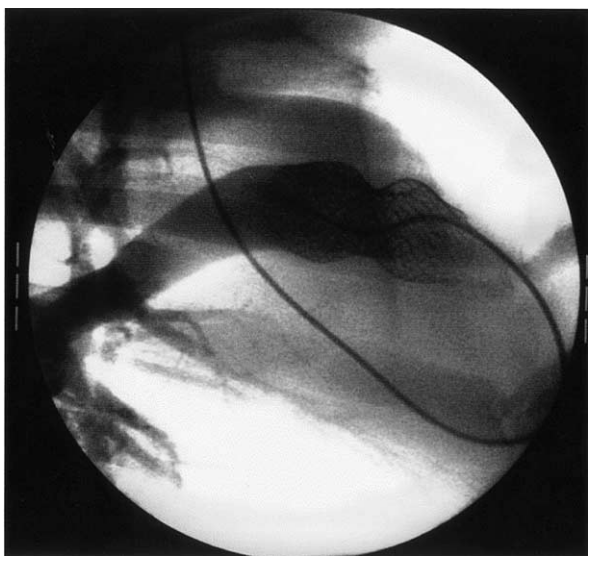

Figure 3. Angiogram showing the perfect competence of the 18-mm implanted valve (equivalent of a lateral view). Note the size of the pulmonary artery trunk as compared with the size of the restricted area where the valve is located.

DISCUSSION

Patients who underwent transannular patch repair of TOF during infancy can have pulmonary trunks that often exceed 30 mm in diameter, making percutaneous implantation technically impossible with the current approach (1–3,7–9). We have proposed various solutions to resolve this problem. First, it is possible to implant two Numed valved stents—one in each PA. However, this solution will be expensive, will increase the duration of the procedure, and will not eliminate blood regurgitation from the pulmonary trunk. More interestingly, cooperation between surgeons and cardiac interventionists would permit a stepwise implantation without requiring extracorporeal circulation. Through a thoracotomy, the PA could be banded, allowing for subsequent percutaneous implantation of a pulmonary valve. None of these solutions is fully satisfactory. Therefore, investigations into other valves and/or technologies were required in order to make this technique available for this patient group.

In our previous experience, we used a balloon-expandable vascular stent. The wires are made of a soft and highly malleable alloy consisting of platinum and iridium. In our in vitro studies, we found that the current wire design could interfere with valve geometry and function when used at large diameters. Therefore, we investigated the two-step deployment strategy, as we have previously reported in our successful aortic valve implantation (4). As in this experience, we combined a self-expanding nitinol stent with a balloon-expandable stent. A single stent based solely on the use of the nitinol technology was also investigated as a one-step deployment strategy. We thus designed a self-expandable stent with two different diameters. The diameter of its extremities is slightly larger than the diameter of the pulmonary trunk to allow for a mechanical fixation to the wall of the vessel. Because only 18-mm valves were available for this experiment, the middle part of the stent was calibrated to shelter this valve size. However, with the use of other valves, this stent can be manufactured at various lengths and diameters to encompass all clinical situations.

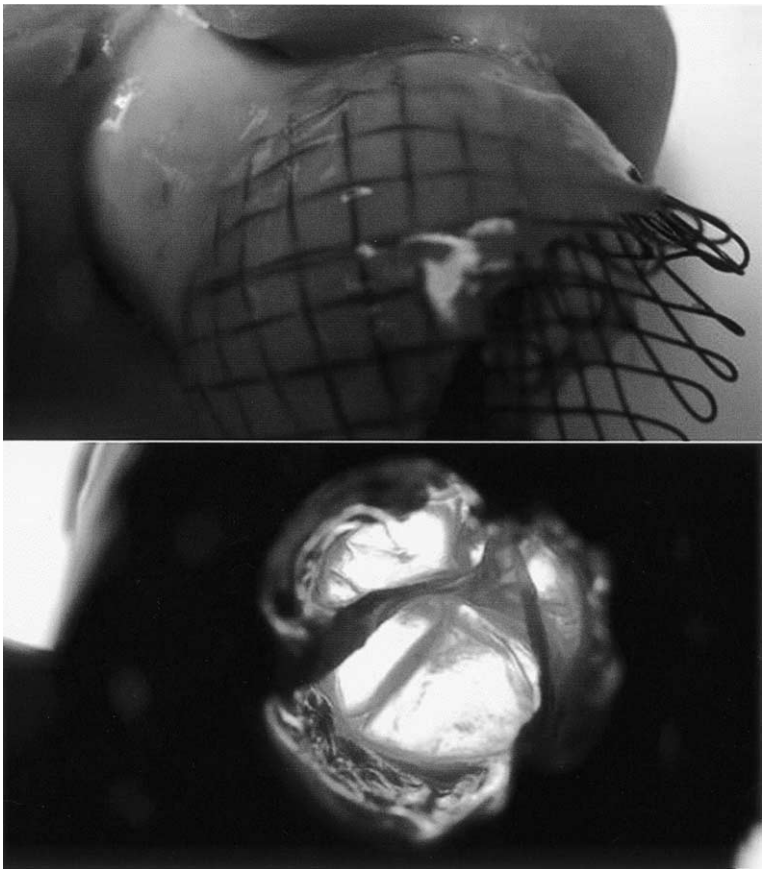

Figure 4. Macroscopic views showing a newly designed, valved nitinol stent explanted two months after implantation. Note the fibrous covering of the nitinol wires and the thin valve inside the stent.

In the present study, implantation of these newly designed stents was feasible in eight of 10 ewes (one additional animal received an intravascular non-valved reducer). As in our initial report in 2000, we failed to implant two valved devices because of the narrow angle between the tricuspid valve and the RV outlet. In humans, the large size of the femoral vein allows for a straighter catheter course and consequently reduces the risk of technical failure. Thus, since 2001, we have attempted and succeeded in replacing the pulmonary valve in 23 of 24 patients. The use of this new device should not be different in terms of the rate of successful delivery.

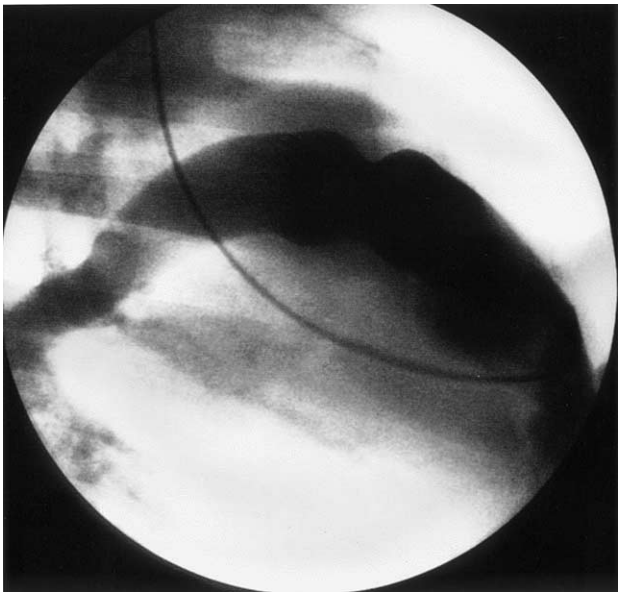

Figure 5. Lateral view of right ventriculogram showing perfect sealing of the device.

The implantation of the downsizing stent permitted the reduction of the pulmonary trunk to the desired diameter, with only a slight elevation of RV pressure, similar to the one seen with a mechanical prosthesis. This elevation did not increase in animals with late-sacrifice time points. A similar reduction of diameter by creating an obstruction to the RVOT could have repercussions on RV function in patients with a long-standing history of pulmonary regurgitation. Therefore, we investigated the possibility of preceding with the insertion of a valve by implantation of a non-valved, downsizing stent. In humans, this setting would allow one to verify the absence of an inappropriate elevation in RV pressures before considering a valve implant. In our protocol, we delayed valvular implantation in the second group to limit the risk of embolization of the device, but this implantation could probably be done during

a single procedure after confirming that the reduction in diameter is well tolerated.

Study limitations and unanswered questions. First, in the present study, only animals with a normal RVOT were evaluated. Because the aneurysmal dilation of the RVOT, as seen in TOF patients, appears late after surgical repair, a similar setting was impossible to achieve in animals. In these patients, deployment of a self-expandable stent would be hampered. Placement of a downsizing stent in a nonsymmetrical RVOT might therefore be an issue. Obstruction in deployment could theoretically be responsible for a partial deployment, with lengthening of the device and an overall reduction of diameter. The central part, in particular, would have a smaller diameter than expected and could create an additional obstruction to flow, interfering with the valve geometry and function. However, the designed stent had an intrinsic radial force that allows for complete deployment when external forces are limited, as expected in aneurysmal RVOT. Moreover, each part of the stent—namely, the proximal and distal extremities and the restricted area, even if they are connected—has its proper force and can be deployed completely if one among them is forced. Thus, if a part is incompletely deployed due to an external constraint that is too significant, the two others can be deployed normally. In practice, only the ends of the stent, whose diameter borders that of the RVOT, can be constrained. However, in patients with tortuous pulmonary anatomy, where incomplete deployment of the device is expected, asymmetrical devices with three different diameters for each part of the stent can be manufactured and used. A stepwise approach, as reported here in group 2, would also be indicated. In that case, a balloon-expandable stent, in addition to supporting the valve, would advantageously add radial forces, allowing for complete deployment of the nitinol stent.

Another concern is the evolution of the thrombus formation found between the stent and PA wall as a consequence of the "no-flow" and blood entrapment. Although not found in our animal experiment, a risk of thromboembolism exists. However, the risk is limited as long as the device is perfectly sealed. After a short time, the thrombus is organized and unlikely to migrate. Over a period of time that formation might regress, as seen in our experiment and reported in aneurysms of the aorta treated with a covered stent. However, long-term studies will be necessary to address this question more accurately.

Conclusions. Herein, we report new insights into pulmonary valve replacement through a transcatheter technique. We resolved the problem of implantation in a large RVOT by designing a new stent made of nitinol wires. This device allows for a size reduction of the pulmonary trunk to a diameter that permits percutaneous valve replacement during the same procedure or two months later. The future availability of this device for human application will lead to the extension of the present indications to transcatheter replacement of the pulmonary valve, regardless of the PA size.

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