Evolving Technology

Off-pump replacement of the pulmonary valve in large right ventricular outflow tracts: A hybrid approach

Younes Boudjemline, MD[a,b,c]
Silvia Schievano, MD[c]
Caroline Bonnet, MD[a]
Louise Coats, MD[c]
Gabriella Agnoletti, MD[a]
Sachin Khambadkone, MD[c]
Damien Bonnet, MD[a,b]
John Deanfield, MD[c]
Daniel Sidi, MD[a,b]
Philipp Bonhoeffer, MD[c]

Background: Percutaneous pulmonary valve replacement has recently been introduced and is under investigation in humans. This technique is, however, limited to patients with a right ventricular outflow tract that does not exceed 22 mm in diameter. We report our experience of off-pump pulmonary valve replacement using a hybrid approach in animals with large right ventricular outflow tracts.

Methods: Eight ewes were included in the protocol and were equally divided into 2 groups. A left thoracotomy was first performed, and the main pulmonary artery was banded by using 2 radiopaque rings with a diameter of 18 mm that allowed for further pulmonary valve replacement. We then intended to implant a valved stent either percutaneously (group 1) or through a transventricular approach (group 2). All animals were killed after valve implantation. The operation allowed the pulmonary diameter to be reduced from 30 to 17.6 mm.

Results: The right ventricular pressure did not significantly increase after reduction of the pulmonary artery diameter (25 vs 36 mm Hg). Subsequent pulmonary valve replacement through a percutaneous or a transventricular approach was always possible without any requirement for extracorporeal circulation. All devices were successfully delivered inside the pulmonary artery banding and were functioning perfectly at early evaluation.

Conclusions: Implantation of a pulmonary valve is possible in ewes through a hybrid approach when the right ventricular outflow tract exceeds 22 mm in diameter. This involves both surgeons and interventionists and allows for a staged procedure in which the valvulation is performed percutaneously or, for a combined hybrid approach, in which the valve is implanted off pump transventricularly during the same operation.

From the Service de Cardiologie Pédiatrique, Hôpital Necker Enfants Malades, Paris, France,[a] Institut National de la Santé et de la Recherche Médicale EMIU 0016, Faculté de Necker Enfants Malades, Paris, France,[b] and Cardiothoracic Unit, Great Ormond Street Hospital, London, United Kingdom.[c]

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Address for reprints: Younes Boudjemline, MD, Service de Cardiologie Pédiatrique, Hôpital Necker Enfants Malades, 149 rue de Sèvres, 75015 Paris Cedex, France (E-mail: younes.boudjemline@nck.ap-hop-paris.fr).

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Percutaneous pulmonary valve replacement has recently been introduced, and early clinical human experience has been reported.[1-6] The device we developed is a biological valve harvested from the bovine jugular vein and mounted in a balloon-expandable stent. Because of valve availability, indications in humans are presently limited to patients who have a right ventricular outflow tract (RVOT) that does not exceed 22 mm in diameter. Unfortunately, patients who underwent transannular patch repair of tetralogy of Fallot during infancy can have pulmonary trunks that often exceed 30 mm in diameter, and this makes percutaneous implantation technically impossible with the current approach.[1-3,7-9] These patients are the most common group of patients who require pulmonary valve replacement. To broaden the indications of percutaneous replacement of the pulmonary valve to the entire anatomic spectrum of pulmonary regurgitation, we recently reported the use of a self-expandable stent that allows downsizing the diameter of the vessel to the available valve diameter.[10] In tortuous pulmonary anatomy, as frequently seen after surgery in patients with a tetralogy of Fallot, the deployment of such a stent could be hampered. To encompass this problem, we imagined a hybrid approach that involved both surgeons and cardiac interventionists in which the first step would be to surgically perform a pulmonary artery (PA) banding to a diameter that allows for a further pulmonary valve replacement (PVR). We therefore designed an experimental study to evaluate this alternative strategy aiming at the off-bypass implantation of a valved stent in pulmonary position in large RVOTs.

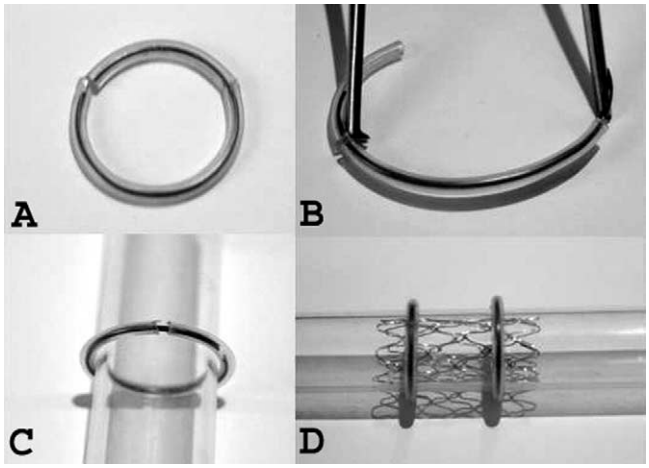

Figure 1. In vitro views of the various phases of the procedure. A, The ring used for the pulmonary artery banding is made of nitinol and has a spontaneous diameter of 18 mm. B, The ring is opened and straightened before its passage around the main pulmonary artery, represented by the glass tube. C, View showing the aspect of the ring around a glass tube. D, View showing the aspect of a stent placed inside the glass tube after placement of 2 rings.

Methods

Device Preparation for Downsizing the Diameter of the Pulmonary Trunk

Two rings made of a 0.27-mm self-expandable alloy wire encapsulated in a plastic tube were prepared (AMF, Reuilly, France; Figure 1). The rings had a spontaneous diameter of 18 mm and were "opened." This allowed for the structure to be straightened and placed around the PA. These radiopaque rings were designed to support the valved stent and to help its precise placement under fluoroscopic guidance.

Preparation of the Valved Stent for PVR

The valved stent was prepared as previously reported with the use of an 18-mm bovine jugular venous valve mounted in a balloon-expandable CP stent (NuMED Inc, Hopkinton, NY).[1]

The Delivery System

The delivery system consisted of a front-loading long sheath premounted with a 22-mm balloon-in-balloon catheter inside (NuMED). The distal part of the sheath was larger than the proximal part, thus liberating extra space for valved stent placement. The outer size of the delivery system was 18F distally and 14F proximally. The length of the distal part was 5 cm. The sheath freely slid over the device. 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 or ventricle at the time of insertion.

Repartition of the Animals and Grouping

Eight ewes weighing 60 to 70 kg were included. Animals were equally divided into 2 groups regarding the type of hybrid approach. All animals had a surgical reduction of the PA diameter through a thoracotomy by using the device described previously without cardiopulmonary bypass. In the first group (4 animals), we then intended to implant an 18-mm valved stent percutaneously through the left jugular vein. In the second group (4 animals), we expected to implant a valve through a small right ventriculotomy into the previously placed PA banding by using the same thoracotomy. This study was approved by the ethical committee of our institution, and animals received care in accordance with the "Principles of Laboratory Animal Care" and the "Guide for the Care and Use of Laboratory Animals."

PA Banding

Ewes were sedated with intravenous injection of thiopental sodium (Pentothal; 10 mg/kg body weight), placed in the lateral position, intubated, and ventilated with 100% oxygen and 1% halothane. Anesthesia was maintained with halothane (0.5%-3%). Cardiac and respiratory functions were monitored throughout the procedure. A left thoracotomy was performed in the fourth intercostal space. After the thoracotomy was completed, all ewes underwent catheterization for anatomic and hemodynamic evaluations before PA banding. For that purpose, the left jugular vein was prepared for catheterization, and a 7F sheath was introduced. Heparin (100 UI/kg) was administered once after thoracotomy and vascular

TABLE 1. Hemodynamic data before pulmonary artery banding

Animal no.	Diameter of the main pulmonary artery (mm)	RVP (mm Hg)*	PAP (mm Hg)†	PAo (mm Hg)†
1	30	20/0/6	19/9/12	103/62/75
2	32	22/0/8	22/13/16	95/56/69
3	31	28/0/4	28/11/17	110/65/80
4	28	30/0/5	27/11/16	94/58/70
5	30	25/0/5	24/12/16	115/65/82
6	29	28/0/7	25/10/15	114/68/83
7	32	25/0/6	23/8/13	89/54/66
8	28	24/0/4	24/14/17	108/57/74
Mean	30	25.3/0/5.9	24/11/15.3	103.5/60.6/74.9
SD	1.6	3.3/0/1.5	2.8/2/1.8	9.8/5.1/6.3

RVP, Right ventricular pressure; *PAP,* pulmonary artery pressure; *PAo,* aortic pressure.
*Data are systolic/diastolic/end-diastolic.
†Data are systolic/diastolic/mean.

access were obtained. A ring was straightened and inserted proximally around the main PA. A second ring was then placed 2 cm more distally than the first one. Particular attention was taken not to traumatize the vessel and the surrounding structures when passing the rings around the main PA. The rings were then sutured with a discontinuous suture by using a 4-0 propylene thread anteriorly to disable their displacement during stent implantation. These sutures did not, however, impinge the possibility for the ring to open when dilated with a balloon of a larger diameter. Because of the intrinsic properties of the material used to manufacture the bandings, each ring tends to recover its spontaneous diameter, thus adding some dynamic support for the valve to be implanted.

Pulmonary Valve Insertion

In both groups, the valved stent was loaded into the previously described 18F delivery system (NuMED). In group 1, the loaded delivery system was inserted through the jugular vein over a previously positioned 0.035-inch extrastiff guidewire (Amplatzer; AGA Medical Corporation, Golden Valley, Minn). The stent was advanced, uncovered, and deployed in the pulmonary trunk between the 2 markers of the PA banding by subsequently inflating the inner and the outer balloon catheters. After valve insertion, the balloons were finally deflated and retrieved with the delivery system. The valved stent was left in the deployed position. In animals from group 2, a 10-mm large purse-string suture was performed with 4-0 polypropylene approximately 3 cm below the native pulmonary valve. The right ventricle was punctured in the middle of that purse in the direction of the PAs, and a wire was inserted in the lumen of the needle, advanced in the right PA, and exchanged for a right coronary catheter (Cordis, Montargis, France). Under fluoroscopic guidance, a 0.035-inch extrastiff guidewire (Amplatzer) was positioned in the distal right PA. The valved stent was finally inserted as previously described for animals from group 1. Bleeding was controlled by tightening of the purse string. After the procedure, the ventriculotomy was closed with the suture of the purse.

Cardiac Catheterization and Testing of the Implanted Device

Right ventricular and pulmonary pressures were measured before and after PA banding and after the implantation of the valved stent to determine the gradient across the banding and the stent. Angiographic evaluation consisted of pulmonary injection and right ventriculography. Angiograms were performed (1) before the procedure, to define the anatomy of the pulmonary root and to measure the size of the pulmonary trunk; (2) after PA banding; and (3) before the animals were killed, to confirm the appropriate position of the valved stent and its sealing and to verify the function of the implanted valve.

Graft Retrieval

All animals were killed 1 hour after the valve implantation. Before harvesting, heparin (300 UI/kg) was given intravenously. The heart and the lungs were retrieved together in 1 block. The pulmonary vascular tree was examined to determine the position of the implanted device in relation to the PA banding. The device and the band were 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 fluid in the graft.

Results

The mean size of the pulmonary trunk was 30 ± 1.6 mm (range, 28-32 mm; Table 1). PA banding was possible in all 8 ewes without any macroscopic damage to the main PA or the surrounding structures. After the left thoracotomy was performed, the PA banding was achieved in less than 30 minutes in all animals (Figure 2). The mean diameter of the main PA decreased significantly to 17.6 ± 0.5 mm ($P < .00001$). The right ventricular systolic pressure increased from 25 ± 3 mm Hg to 36 ± 6 mm Hg ($P = .003$; Table 2). The PA pressures decreased slightly from 24/11/15 mm Hg to 22/10/14 mm Hg (systolic/diastolic/mean) after creation of the band ($P = .27$, .39, and .22, respectively).

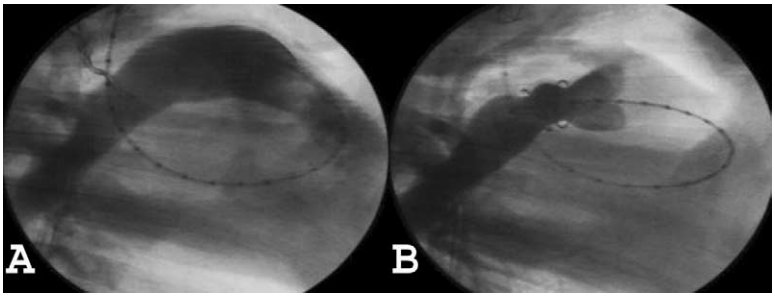

Figure 2. Angiograms before (A) and after (B) the pulmonary artery banding, showing the reduction of the diameter and the radiopaque marker of the rings.

TABLE 2. Hemodynamic data after pulmonary artery banding

Animal no.	Diameter of the main pulmonary artery (mm)	RVP (mm Hg)*	PAP (mm Hg)†	PAo (mm Hg)†	RV to PA systolic gradient (mm Hg)
1	18	38/0/5	18/10/13	96/49/65	20
2	17	44/0/8	18/12/14	110/55/73	26
3	18	36/0/6	22/10/14	107/58/74	14
4	17	34/0/5	27/12/17	88/55/66	7
5	17	38/0/4	20/8/12	124/63/83	18
6	18	30/0/8	27/11/16	92/49/63	3
7	18	42/0/6	18/9/12	113/62/79	24
8	18	26/0/5	26/10/15	98/54/67	0
Mean	17.6	36/0/5.9	22/10.2/14.1	103.5/55.6/71.3	14
SD	0.5	6/0/1.5	4.1/1.4/1.8	12.1/5.2/7.2	9.7

RVP, Right ventricular pressure; *PAP,* pulmonary artery pressure; *PAo,* aortic pressure; *RV,* right ventricle; *PA,* pulmonary artery.
*Data are systolic/diastolic/end-diastolic.
†Data are systolic/diastolic/mean.

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All 8 devices were successfully implanted by using a 22-mm balloon catheter. After vascular access was granted, mean procedural times in animals from groups 1 and 2 were 10 minutes (range, 8-15 minutes) and 6 minutes (range, 4-7 minutes), respectively. The mean diameter of the main PA increased significantly after PVR to 21.1 ± 0.8 mm as compared with postbanding ($P < .00001$) and prebanding ($P < .00001$) procedures. The mean systolic transprosthetic gradient was 14 ± 9.7 mm Hg (range, 0-26 mm Hg; Table 1). This gradient decreased when comparing postbanding and post-PVR evaluations (6.4 ± 2.1 mm Hg vs 14 ± 9.7 mm Hg) but remained significantly higher than basal data (6.4 ± 2.1 mm Hg vs 1.25 ± 1.3 mm Hg; Tables 3 and 4). The mean ratio between the right ventricular and aortic pressures was less than 35% (27.8% ± 3.6%) in all animals (range, 24%-34.7%; Table 3). There was no early migration of any valved stents.

Angiographic evaluation revealed that the implants were in the desired position (Figure 3) between the 2 radiopaque markers and confirmed the sealing of the device, showing no leak between the valved stent and the banded pulmonary wall. Valves were competent angiographically and hemodynamically (Figure 3). As expected, at autopsy, a small hematoma of the pulmonary wall was found underneath the rings in all animals (Figure 4). No extravasation of blood was found. Inspection of implanted valves showed thin and mobile leaflets.

Discussion

Patients who have undergone transannular patch repair of tetralogy of Fallot during infancy have pulmonary trunks that often exceed 22 mm in diameter, and this makes percutaneous implantation technically impossible with the current approach.[1-3,7-9] To encompass this difficulty and to broaden the indications of percutaneous pulmonary valve implantation to the entire spectrum of patients, we designed and recently reported the use of a preshaped self-expandable stent that has 2 different diameters. This stent was constructed from a nitinol wire in the shape of a conduit with a central restriction of its diameter (AMF). The extremities had a spontaneous diameter of 30 mm, and the central restricted part was calibrated to shelter an 18-mm valve. The overall length of the deployed device was 5.5 cm, and the restricted part measured 15 mm. A polytetrafluoroethylene membrane was sutured on the device to ensure the sealing of the device. In reported experiments, implantation of these

TABLE 3. Hemodynamic data after pulmonary valve insertion

Animal no.	Diameter of the main pulmonary artery (mm)	RVP (mm Hg)*	PAP (mm Hg)†	PAo (mm Hg)†	RV to PA systolic gradient (mm Hg)	Type of implantation
1	20	25/0/7	16/11/13	104/62/76	9	P
2	21	26/0/7	19/13/15	98/52/67	7	TV
3	20	28/0/5	20/12/15	100/60/73	8	P
4	21	29/0/6	25/11/16	94/58/70	4	TV
5	22	28/0/5	22/10/14	108/62/77	6	P
6	22	30/0/7	24/12/16	104/60/75	6	TV
7	21	27/0/5	24/14/17	110/60/77	3	P
8	22	33/0/6	25/12/16	95/50/65	8	TV
Mean	21.1	28.3/0/6	21.9/11.9/15.3	101.6/58/72.5	6.4	
SD	0.8	2.5/0/0.9	3.3/1.2/1.3	5.8/4.5/4.7	2.1	

RVP, Right ventricular pressure; *PAP,* pulmonary artery pressure; *PAo,* aortic pressure; *P,* percutaneous; *TV,* transventricular; *RV,* right ventricle; *PA,* pulmonary artery.
*Data are systolic/diastolic/end-diastolic.
†Data are systolic/diastolic/mean.

TABLE 4. Comparison among hemodynamic data obtained before the procedure, after PA banding, and after pulmonary valve insertion

Variable	Base	After PA banding	After valve insertion	*P* value
Diameter of the MPA (mm)	30 ± 1.6	17.6 ± 0.5	21.1 ± 0.8	<.00001*
RVP systolic (mm Hg)	25.3 ± 3.3	36 ± 6	N/A	.0003
RV to PA systolic gradient (mm Hg)	1.25 ± 1.3	N/A	6.4 ± 2.1	<.0001
PAP diastolic (mm Hg)	N/A	10.2 ± 1.4	11.9 ± 1.2	.024

Data are mean ± SD. All data from Tables 1 to 3 were compared 2 by 2 (base × PA banding, base × valve insertion, and PA banding × valve insertion). Only statistically significant data are shown in this table. *MPA,* Main pulmonary artery; *RVP,* right ventricular pressure; *N/A,* not applicable; *PAP,* pulmonary artery pressure; *RV,* right ventricle; *PA,* pulmonary artery.
*Significant for all 3 comparisons.

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stents was feasible in nearly all included ewes, thus permitting the reduction of the pulmonary trunk to the desired diameter with only a slight increase of right ventricular pressure.[10] Despite excellent preliminary results, several limitations to the study urged us to develop alternative approaches. The anatomy of the RVOT varies greatly between patients, and tortuous pulmonary anatomy is not infrequently seen in patients who undergo operation in infancy for tetralogy of Fallot after long-standing pulmonary regurgitation. During the last year, we have been imaging many of these patients and have tried to virtually implant this device (data not shown). In approximately 50% of patients, the device as initially designed was considered implantable.

Elsewhere, its deployment was unsatisfactory because of tortuous anatomy with a great change in diameter throughout the length of the main pulmonary artery, shortness of the main pulmonary artery, or both. These drawbacks led to partial deployment, lengthening, overall diameter reduction, and inappropriate sealing of the device with periprosthetic leakage. During use of a valved device, the restriction of the central part could additionally interfere with valve geometry and function. We therefore investigated alternative approaches and hypothesized that a hybrid approach with cooperation between surgeons and cardiac interventionists would permit a stepwise implantation without necessitating extracorporeal circulation. Through a left thoracotomy, the PA was banded by using 2 radiopaque rings; this allowed for subsequent off-pump implantation of a pulmonary valve. We then investigated the possibility of inserting the valve during the thoracotomy through a right ventriculotomy or after the thoracotomy through a percutaneous approach. We succeeded in inserting a pulmonary valve by using both approaches with only a slight increase of the right ventricular pressure: all right ventricular pressure was less than 33 mm Hg. That kind of increase should have limited repercussions even in patients with a failing right ventricle. In patients with preexisting increased right ventricular pressure, any additional obstruction could be deleterious. This should be avoided by aggressively treating significant PA stenosis before PVR.

In humans, both approaches could be similarly used. Each procedure has specific drawbacks and advantages. We, however, favor the transventricular approach because (1)

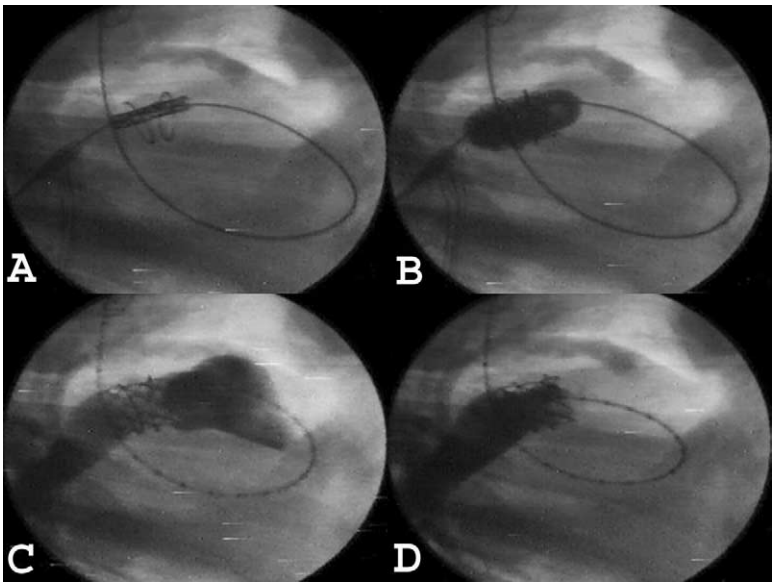

Figure 3. Angiograms showing the implantation of the valved stent through a percutaneous approach (group 1). A, The valved stent has been advanced from the jugular vein in the main pulmonary artery. B, The balloons are inflated to expand the stent. C, Proximal angiogram showing the sealing of the device. D, Distal angiogram demonstrating the competence of the implanted valve.

banding and valvulation are performed during the same procedure; (2) rescue extracorporeal circulation can be performed faster; and (3) the stent can be secured by stitches, thus limiting the risk of secondary stent migration. Scarring on the right ventricle does not seem to be a problem because the right ventriculotomy can be performed on the site of the previous ventriculotomy. In patients with no history of surgery, a percutaneous approach during the operation or after recovery should be preferred to the transventricular approach to avoid the risk of late arrhythmia and sudden death, which might result from a right ventriculotomy.

This study had several limitations. First, only animals with normal RVOTs were evaluated. Because the aneurysmal dilatation of the RVOT as seen in Fallot patients appears late after surgical repair, a similar setting was impossible to achieve in animals. Similarly, Fallot patients are often operated on several times, and this makes the chest opening and dissection more difficult each time. The creation of the banding could, in theory, be difficult in such situation because of the size discrepancy between the native RVOT and the banding to be created and because of the previous interventions. This needs to be addressed before human application. Second, the investigated approaches do not retrieve the aneurysmal and akinetic RVOT. This could limit the improvement of the right ventricular function of the patients and would favor on-pump surgical procedures with resection of the aneurysmal part. This should, however, be balanced by the repercussions of cardiopulmonary bypass on ventricular function. Moreover, the superiority of PVR with resection of the aneurysmal RVOT over PVR without remodeling of the RVOT has not been clearly established.[11] Randomized controlled studies will be necessary to address this question in which various techniques, including the off-pump hybrid approach and on-pump PVR with and without remodeling of the RVOT, should be compared prospectively. Third, because no chronic data are available, the long-term performance of this approach remains unknown and requires more experimental studies before human application. In particular, the risks of secondary erosion and migration of the rings and valved stents should be assessed more accurately. However, both theoretical risks of migration can be reduced or canceled. For insertion of each ring around the PA, limiting the dissection of the PA posteriorly to 2 small spaces rather than 1 large space is a way to limit the tendency of the bands to migrate. Additionally, suturing the rings to the anterior wall of the PA, as we did, might also reduce the risk of band migration. Similarly, to avoid stent migration, it can be secured by stitches at the level of the rings at the time of the implantation. Flaring the end part of the stent by using a larger balloon might additionally help to reduce this risk.

In conclusion, here we report new insights into PVR through a hybrid approach. We resolved the present limitation of percutaneous implantation in the large RVOT by first reducing the diameter of the RVOT. This approach does not require cardiopulmonary bypass and allows for further pulmonary valve insertion, either percutaneously or through a small ventriculotomy. This study provides technical infor-

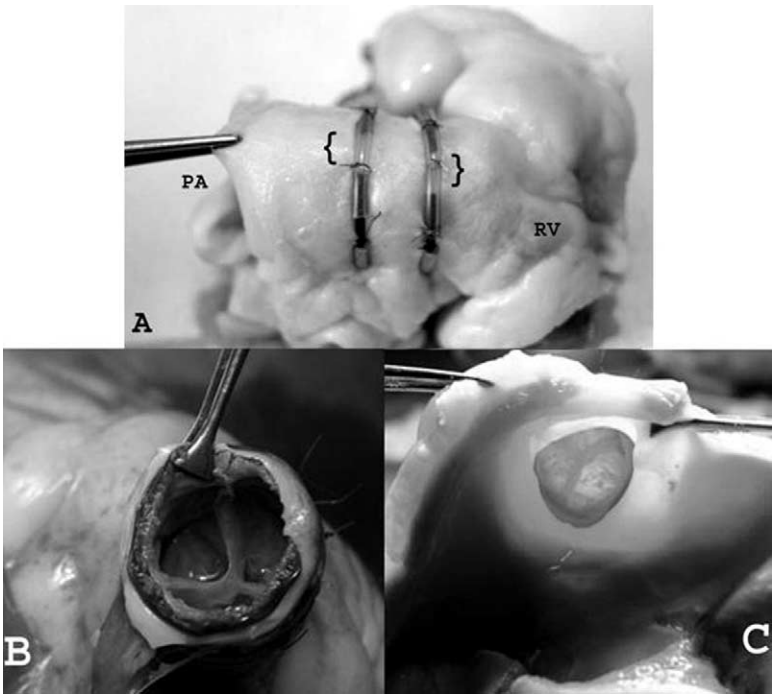

Figure 4. Macroscopic views showing the external aspect of the main PA after harvesting (A) and the coaptation of the leaflet of the implanted valves from the pulmonary artery (B) and the right ventricle *(RV)* (C). Note on (A) the opening of the rings resulting from the discrepancy between the spontaneous diameter of the ring (18 mm) and the diameter of the valved stent (22 mm). The rings, because of their intrinsic properties, tend to return to their diameters, thus giving some dynamic forces to the support.

mation regarding the method of RVOT modification and valve implantation, but long-term performance was not evaluated and will require further long-term studies before clinical application. If applicable in humans, this approach will lead to the extension of the present indications to off-pump replacement of the pulmonary valve by using the available device, regardless of the size and anatomy of the PA.

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