Development of a device for transcatheter pulmonary artery banding: evaluation in animals

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Introduction
Pulmonary artery banding (PAB) was introduced in 1952 as a palliative procedure for patients with congenital heart defects characterized by increased pulmonary blood flow and pressures.1 Despite the tremendous development of surgical techniques and cardiopulmonary bypass, PAB remains the preferred palliation to delay the later repair of intracardiac defects in infancy or childhood. The technique is now well codified and rules exist to determine the length of the band in relation to the underlying defect as well as the body weight of the patient.2 Furthermore, PAB has been recently offered to patients with late referral of transposition of the great arteries and with congenitally corrected transposition of the great arteries.3–6 In those patients, double switch operation is one of the surgical options, but the left ventricle (LV) pumping in the pulmonary circulation needs to be retrained in order to assume the systemic work load.7,8 Finally, new indications have been considered for neonates with hypoplastic left heart malformations.9–12 Optimal tightening of the band is, however, still problematic. Some patients need PAB revision because of excessive or insufficient tightening. These re-operations are associated with increased morbidity and mortality. To overcome these difficulties, several attempts have been made to develop a transcatheter PAB; most of them being temporary devices but to date none have a clinical application.13–15 Therefore, surgery remains the only way to perform a PAB. We developed a device for intravascular PAB. We report here the preliminary experimental application of this device.

Aims Pulmonary artery banding (PAB) is the first palliation in infants with complex congenital heart disease and elevated pulmonary blood flow. In older patients with corrected transposition of the great arteries, it may be used to retrain the left ventricle. To date, the only option is surgical. We report the development and the evaluation of a device for transcatheter PAB.

Methods and results We intended to implant a pulmonary artery (PA) reducer percutaneously between the native pulmonic valve and the pulmonary bifurcation. Immediately following its insertion, we planned to implant a balloon expandable stent inside the restriction to calibrate the banding. Sheep were sacrificed acutely (group 1, n = 6) and after 1 month of follow-up (group 2, n = 6), the reducer was implanted successfully in all animals. It allowed the PA diameter to be reduced from 25 to 10.5 mm. Bare stents were successfully delivered inside the reducer. No paraprosthetic leak was found by injecting contrast dye. After the insertion procedure, signs of intolerance to obstruction were present in all animals and prompted us to dilate the stents from 12 to 16 mm. One animal from group 1 died before a balloon dilatation could be achieved. In the animals from group 2, the mean systolic gradient was 19 and 34.8 mmHg, respectively, at early and late evaluation.

Conclusion Implantation of a PA reducer is possible in sheep, through a transcatheter approach allowing intravascular PAB. Miniaturization of the device is necessary to enlarge its use from adulthood to childhood.

Methods
Device preparation for downsizing the diameter of the pulmonary trunk
We designed and developed a self expandable stent constructed from a single 0.22 mm nitinol wire in the shape of a conduit with a central restriction (AMF, France). Both extremities come back to the middle of the central restriction and in parallel to this part, realizing a double conduit as shown in Figure 1. The overall lengths of the deployed and cramped device were, respectively, 2 and 5.5 cm. The ends had a spontaneous diameter of 30 mm and the central restricted part had a diameter of 15 mm. To guarantee the perfect sealing of this device, we sutured a 0.1 mm PTFE membrane, usually used for covered stent (AMF, France) with a 4.0 propylene thread on the inner part of the device (Figure 1).
On the right panel, the device is shown covered with a PTFE membrane. Figure 1 The newly designed stent is shown uncovered (lateral view, left panel). The extremities have a diameter of 30 mm, whereas central part is 15 mm. On the right panel, the device is shown covered with a PTFE membrane.

Repartition of the animals
Totally, 12 sheep weighing 50–60 kg were included. Animals were equally divided into two groups. Animals from group 1 (six animals) were sacrificed 1–2 h after stent implantation and animals from group 2 (six animals) were sacrificed after a follow-up of 1 month. We intended to implant a 30 mm device as a first step, immediately followed by the insertion of a balloon expandable bare stent.

Percutaneous reduction of the diameter of the pulmonary trunk
All sheep underwent catheterization for intravascular reduction of the pulmonary artery (PA) trunk under general anaesthesia. Anaesthesia was induced with 10 mg/kg of thiopental and maintained with halothane in mechanically ventilated sheep. Heparin (100 IU/kg) was administrated once during the procedure. Animals from group 2 did not receive any long-term anticoagulation. All animals were treated according to the European regulations for animal experimentation.16

Through the right jugular vein, a 5 French right Judkins coronary catheter (Cordis, Issy les Moulineaux, France) was advanced in the distal PA. Through this catheter, a 0.035 inch extra-stiff guide wire (Amplatzer, Golden Valley, USA) was positioned distally. The reducer was loaded into a 16-Fr Mullins sheath (Cook, France), inserted over the previously positioned wire and advanced into the PA. The deployment was performed by pulling on the external sheath while maintaining the dilator in position. We then pushed the sheath forward while holding the whole system together to configure the proximal part. This had the effect of inverting the distal part of the reducer. In that configuration, the distal part was applied to the pulmonary wall and surrounding the distal part of the sheath. The tubular part of the reducer was subsequently delivered, followed by the proximal part. Its final configuration was obtained by pulling on the sheath while maintaining the wire position. After the complete delivery of the reducer, the Mullins sheath was retrieved leaving the device and the wire in position. We intended to place the reducer between the native pulmonic valve and the PA bifurcation. For animals from chronic group, a careful attention was taken not to impinge on pulmonary valve function since the creation of a pulmonary insufficiency can be deleterious.

Adjustment of PA diameter
PA diameter was adjusted to obtain a slight elevation of the right ventricular pressure (RVP) compatible with a chronic study. Three parameters were considered for adequate tightening. The systolic transprosthetic gradient was judged satisfactory if it did not exceed 25 mmHg. The ratio between the systolic RVP and aortic pressure (AoP) was also taken into consideration. Based on the previous work on PAB (unpublished data), we fixed the upper limit of this ratio at 0.5. Finally, the reduction of the systolic AoP needed to be less than 20% since we noticed that, when a banding was too tight, there was usually a systemic arterial hypotension with a ratio between the systolic RVP and AoP being less than the target number.

To adjust the diameter of the reduction precisely, a bare stent (CP8234, Numed Inc.) was placed within the transcatheter banding system using a conventional technique. Briefly, the bare stent was crimped on a 12 mm balloon catheter (BiB, Numed Inc.). The assembly was loaded in a 12-Fr Mullins sheath (Cook, France), advanced over the same wire, and delivered inside the tubular part of the reducer. Radio-opacity of the reducer was used to position the bare stent. For adjustment, bare stents were dilated with balloon catheters of increasing diameters until fulfillment of the previously described criteria. Briefly, a 14 mm balloon catheter (Tyshak II, Numed Inc.) was advanced over the same wire. When inside the stent restriction, the balloon was inflated to expand the bare stent. The procedure was repeated with a larger balloon if the pressures remained over the desired criteria.

An increment of 2 mm was chosen for the diameter of balloon catheters. Right heart pressures (i.e. RV and PA) were obtained before each balloon inflation to determine the gradient across devices and compared with peripheral systolic AoP. When possible, a steady state of 5 min was obtained before all measurements. Angiographic evaluation consisted of a RV angiography to look for any paraprosthetic leak. Angiograms were performed: (i) before the procedure to define the anatomy of the pulmonary root and to measure the size of the pulmonary trunk; (ii) after final dilatation to confirm the sealing of the reducer. In the chronic group, angiographic and haemodynamic studies were repeated before the sacrifice of the animals.

Graft retrieval
Grafts were explanted acutely in animals from group 1, and 1 month after the initial procedure in animals from group 2. Before harvesting, heparin (300 IU/kg) was given intravenously. The heart and the lungs were retrieved in one block. The pulmonary vascular tree was examined to determine the position of devices in relation to the pulmonary valve. Devices were then harvested with a section of the PA, and rinsed to remove excess intraluminal blood. All devices were inspected.
Results
The mean size of the pulmonary trunk was 24.3 mm ranging from 22 to 27 mm (n = 12). All reducers were successfully implanted. The diameter of the pulmonary trunk was reduced to 10.5 mm (range 8–12 mm).

Animals from group 1
After insertion of the reducer, signs of intolerance to acute intravascular banding (i.e. QRS enlargement, anomalies of the ST-segment, deep decrease of systemic pressure) were present in all animals. The animal with the most important reduction of PA diameter (8 mm) died before any stent placement/balloon dilatation could be achieved. After this death, the delay between reducer placement and stent insertion was reduced by crimping and preparing the stent assembly before the insertion of the reducer and by avoiding haemodynamic assessment after reducer insertion. The placement of the bare stent was possible in all surviving animals (n = 5). Their placement did not require any injection of contrast dye since the reducer acted as a marker. Haemodynamic data are reported in Table 1. At 12 mm, the mean systolic RVP and the ratio between the systolic RVP and AoP increased. Mean systolic AoP decreased in all animals. Therefore, as stated by the protocol, the bare stent was further dilated. We saw a progressive improvement of systolic AoP and tolerance after dilation of the stent from 12 to 16 mm. At 14 mm, QRS were still enlarged and anomalies of the ST-segment still present. At 16 mm, the systolic RVP decreased, but remained slightly elevated when compared with the baseline measurements (P < 0.0001). AoP increased to normal value after this dilation in all animals. Angiographic studies showed that the device was in good position when compared with pulmonary valve and PA bifurcation. Contrast dye perfectly moulded the shape of the reducer without any paraprothetic leak. At autopsy, small haematomas were found on the outer layer of the pulmonary wall in front of the device, but no perforation or blood extravasation was present. The reducer was well-placed in all animals. In particular, pulmonary valve was not impinged and it was distant from the pulmonary bifurcation. As expected, coagulated blood was trapped between different parts of the reducer and the vascular wall.

Animals from group 2
All reducers were successfully implanted (Figure 2). The diameter of the pulmonary trunk was reduced to 10.6 mm (range 10–11.5 mm). All bare stents were successfully inserted within the reducer and were dilated from 12 to 16 mm (Figures 3 and 4). As for animals from group 1, from 10 to 14 mm, intravascular PAB was not well tolerated. No animal died between reducer insertion and stent placement. Acute haemodynamic measurements were in the same range of those obtained in group 1. They are reported in detail in Table 2. At 16 mm, the mean systolic RVP and the ratio between the systolic RVP and the AoP were in the expected range. Mean systolic AoP was normal in all animals. The mean systolic transprosthetic gradient was 19 mmHg. There were no paraprothetic leak found during injection of contrast dye. Post-procedural course was uneventful in all animals.

No device migration occurred during the follow-up. All animals, but one underwent reassessment at 1 month (range 4–6 weeks). One animal died during the follow-up 3 weeks after device insertion. At autopsy, there was no sign of PA erosion or cardiac dysfunction, or thoracic bleeding. Macroscopic vegetations were found on the tricuspid valve and on the proximal part of the device. This severe endocarditis fully explained the death. Elsewhere (n = 5), haemodynamic study showed an increase in systolic RVP, transprosthetic gradient as well as ratio between the systolic RVP and AoP, respectively, to 44.8 mmHg (range 40–52 mmHg, P = 0.0099), 34.8 mmHg (range 27–42 mmHg, P < 0.001) and 0.41 (range 0.29–0.52, P = 0.026) (Figure 5).

On fluoroscopy, no structural damage (i.e. stent fracture) of the device was found. At that point, angiographic evaluation revealed that the implants were in the desired position, and confirmed the sealing of the devices showing no leak between devices and the pulmonary wall.

Autopsies showed a good position of both reducers and stents. No significant damage was found during inspection except in the animal with endocarditis. There was no haematoma around the PA. All devices were completely embedded within a fibrous tissue and fixed to the pulmonary wall. No thrombus was found around any device.

Discussion
PAB is the preferred palliation to delay intracardiac repair of complex congenital heart disease.1–12 It is a surgical procedure performed through a thoracotomy or a mid sternotomy. Besides the difficulty to calibrate the restriction, the procedure is associated with morbidity and mortality and makes further thoracic dissection more complicated. Several attempts have been made to develop a transcatheter PAB. Most of them were non-dedicated devices (i.e. balloon catheter) and inserted temporarily to create an

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Haemodynamic evaluation of animals from group 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
<td></td>
</tr>
<tr>
<td>State</td>
<td>sRVP</td>
</tr>
<tr>
<td>Basal</td>
<td>19.3</td>
</tr>
<tr>
<td>12 mm</td>
<td>40.4</td>
</tr>
<tr>
<td>14 mm</td>
<td>38.6</td>
</tr>
<tr>
<td>16 mm</td>
<td>33.6</td>
</tr>
</tbody>
</table>

sPAP, systolic pulmonary artery pressure; sGradient, systolic transprosthetic gradient; sRVP/sAoP, ratio between systolic right ventricular pressure and systolic aortic pressure; N1, comparison between N1 and basal value, N1 and N2, N1 and N3; NS, not significant.
acute obstruction to the flow. \textsuperscript{13–15} None of these devices have a clinical application.

We investigated the possibility to use a self-expandable stent to reduce the diameter of the PA in order to fashion an intravascular PAB. For this, we designed a stent made of nitinol wire with two different diameters. The diameter of its ends were chosen to be slightly larger than the diameter of the pulmonary trunk. The middle part of the stent was calibrated to reduce the diameter of the PA between 10 and 12 mm. Since the device was slightly oversized to allow for mechanical fixation to the wall, the internal diameter could not be fully predicted in advance. Moreover, because of metal properties, all diameters are fixed in advance making adjustments of the restriction impossible solely with this device. We had the idea of using a bare stent to allow for diameter regulation. The middle part of the device was, therefore, shaped to be able to shelter a balloon expandable stent. Thus, the use of balloon catheter of various diameters theoretically allows a one way adjustment of the reducer. With this design, it is only possible to open the banding but not to close it once it has been opened by a balloon catheter. We tested this hypothesis in 12 animals acutely and during a follow-up of 1 month. Devices were successfully inserted in all animals and were able to reduce the diameter of the PA creating a gradient between the RV and the PA. We encountered two deaths: one acutely and one during the follow-up due to an endocarditis. The latter was related to the inappropriate protocol used for sterilization of devices. The most important problem was related to the inability for the RV to cope

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{image.png}
\caption{Fluoroscopic image showing the reducer in place in the PA (equivalent of a lateral view). Note the size of the PA trunk when compared with the size of the restricted area where the bare stent will be placed.}
\end{figure}
with the acute creation of the afterload. All animals had signs of intolerance with tachycardia, ECG anomalies, and decrease of the systemic pressure and this prompted us to insert and dilate the bare stent inside the reducer to open it.

Limitations to the study and unanswered questions

One limitation of the device is the inability to create a significant elevation of the RVP. This was more related to the underlying heart rather than a problem with the device. The RV was unable, at least acutely, to cope with the increased afterload. We therefore had to relieve a great part of the restriction by opening the band. Unfortunately, the device is not adjustable in both directions. Once opened it is impossible to re-close it. For patients in need of LV retraining, the banding usually needs to be tightened with time to avoid impairment of the LV function. The development of an intravascular device that is fully adjustable would be of value in those patients. However, excluding the Flo Watch system that is available only for a minority of patients weighing between 3 and 10 kg, one should remember that there is, to date, no surgical device that is adjustable.

Even if we did not encounter any device embolization, this is clearly an expected complication because the fixation of the device is only mechanical and not physical. The selection of the device is very important. An oversizing could lead to an inadequate opening of the device or an excessive tightening as we encountered in one animal, whereas an undersizing could be responsible of an embolization. Moreover,
Figure 4 Fluoroscopic view showing the dilatation of the bare stent with a 16 mm balloon catheter.

Table 2 Haemodynamic evaluation of animals from group 2

<table>
<thead>
<tr>
<th>State</th>
<th>sRVP (mmHg)</th>
<th>sPAP (mmHg)</th>
<th>sGradient (mmHg)</th>
<th>sAoP (mmHg)</th>
<th>sRVP/sAoP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal (n=6)</td>
<td>20.8</td>
<td>19.8</td>
<td>1</td>
<td>109.7</td>
<td>0.19</td>
</tr>
<tr>
<td>12 mm² (n=6) basal/14/16</td>
<td>40.3</td>
<td>9.8</td>
<td>10.7/0.0.05/0.003</td>
<td>9.8/0.09/0.05/NS</td>
<td>0.27/0.09/0.01/NS</td>
</tr>
<tr>
<td>14 mm² (n=6) basal/12/16</td>
<td>38.3</td>
<td>11.7</td>
<td>12.0/0.02/NS/NS</td>
<td>12.0/0.02/NS/NS</td>
<td>0.27/0.09/0.01/NS</td>
</tr>
<tr>
<td>16 mm² (n=6) basal/12/14</td>
<td>32.8</td>
<td>14.0</td>
<td>14.0/0.02/NS/NS</td>
<td>14.0/0.02/NS/NS</td>
<td>0.27/0.09/0.01/NS</td>
</tr>
<tr>
<td>16 mm² (n=5) basal/16a</td>
<td>44.8</td>
<td>34.8</td>
<td>34.8</td>
<td>34.8</td>
<td>0.001</td>
</tr>
</tbody>
</table>

n, number of animals; N1 vs basal/N2/N3, comparison between N1 and basal value, N1 and N2, N1 and N3; NS, not significant.

aMeasurements performed acutely.
bMeasurements performed 1 month after the insertion of the device.
even if adequate, it is possible that embolization occurs in particular if the transprosthetic gradient is too important and greater than the strength that holds the reducer in position. There should be a ratio or a formula between the two components. More experimental studies are needed to define more precisely this factor.

Another potential drawback is the incorporation of the device in the pulmonary wall. Surgical correction of the congenital heart disease could be more difficult, needing a reconstruction of the PA because of the presence of the device. However, since the procedure was performed percutaneously, the dissection to liberate the PA would be easier. Moreover, the retrieval of the device in one block with the PA would leave a short gap of 2 cm long that could be repaired either directly by pulling on the pulmonary arteries or, if we are afraid of creating a traction on the PAs, by adding some material to fill the gap. This in our opinion is not a major problem.

Finally, the size of the Mullins sheath required for the reducer insertion is large, excluding the use of such devices for infants and small children. We are working on smaller devices to extend the indications to majority of patients. Further animal studies will be needed.

In conclusion, we report the design and the application in animals of a new self-expandable stent to percutaneously reduce the diameter of the PA in order to create an endovascular PAB. The miniaturization of the device will be needed to extend the indication to infants and children.

Figure 5: RV angiogram on lateral view showing the absence of paraprosthetic leak and the reduction of the PA diameter in one animal from group 2 prior to its sacrifice at 1 month. Note the position of the reducer when compared with the native pulmonary valve (asterisks).
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Conflict of interest: none declared.

References


