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ORIGINAL RESEARCH

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Feasibility Study of Catheter-Based Interventions for Anisotropic Expanded Polytetrafluoroethylene Cardiovascular Conduits in a Growing Lamb Model

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ABSTRACT

Background: Cardiovascular repair in children often requires implant of conduits which do not have growth potential and will require reoperation. In the current study we sought to determine the feasibility of catheter-based interventions of anisotropic conduits inserted as interposition grafts in the main pulmonary artery (MPA) of growing lambs.
Methods: Lambs underwent interpositional implant of either an anisotropic expanded polytetrafluoroethylene (ePTFE) (Test) conduit or conventional PTFE (Control) conduit. In the postoperative period, lambs were anesthetized and underwent catheter-based interventions consisting of hemodynamic and angiographic data collection, balloon dilation and/or stenting of the conduit at 3, 6 or 9 month postoperative time point.
Results: At 3 months, control lambs showed significant increases in right ventricular pressures and trans-conduit gradients in comparison to test lambs. Test conduit diameters were significantly larger compared to controls due to spontaneous radial expansion of the anisotropic conduit. Balloon dilation of test conduits at 3 and 6 months showed a reduction in RV pressure and statistically significant improvement in the RV outflow tract gradient as well as significant increase in graft diameter, compared to both control and pre-dilation conditions. Furthermore, the test conduit diameter increased significantly compared to the pre-balloon and control conditions at each time point. Necropsy of test conduits showed no evidence of tears, perforations, or clot and smooth interiors with well-healed anastomoses.
Conclusions: Anisotropic conduits implanted as interposition grafts in the MPA show spontaneous expansion, and can safely and effectively undergo catheter-based interventions, with significant increases in graft diameter occurring after balloon dilation.

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Growing lamb model; conduits; congenital heart defects; cardiac surgery; balloon dilation; valved stent

Introduction

Surgery for congenital heart disease often requires implantation of conduits for repair, conduits which do not have growth potential and will require multiple repeat interventions or operations [1–4]. There is an ongoing search for bioactive conduits that grow with a patient, potentially eliminating the need for repeated surgical procedures to replace faulty valves and outgrown conduits [5–15]. We have developed a unique cardiovascular conduit with an anisotropic capacity for stretching, by manipulating an expanded polytetrafluoroethylene (ePTFE) polymer sheet with directionally dependent expansion properties. The sheet is circularized in such a way that the resultant tube has expansion potential in a radial direction, requires low pressure to expand its circumference and is easily amenable to having a valve mechanism inserted. In a previous report, we have shown that the resulting anisotropic conduits radially expand spontaneously, as driven by right ventricular pressure in growing lambs, resulting in significantly better right heart hemodynamics compared to controls. These anisotropic ePTFE-based conduits are biocompatible, easily available off-the-shelf, and resist calcification and degeneration [16,17]. The conduit thereby provides a replacement for defective or missing components of the vasculature of a growing child, with potential to radially expand over time to accommodate natural growth. The expansile properties of the conduit may obviate the need for multiple surgeries, or make future catheter-based interventions highly successful.

In the current study, we report the feasibility of catheter based interventions in the form of balloon dilation and stenting. Our findings indicate that anisotropic conduits can be safely and effectively balloon-dilated and stented at

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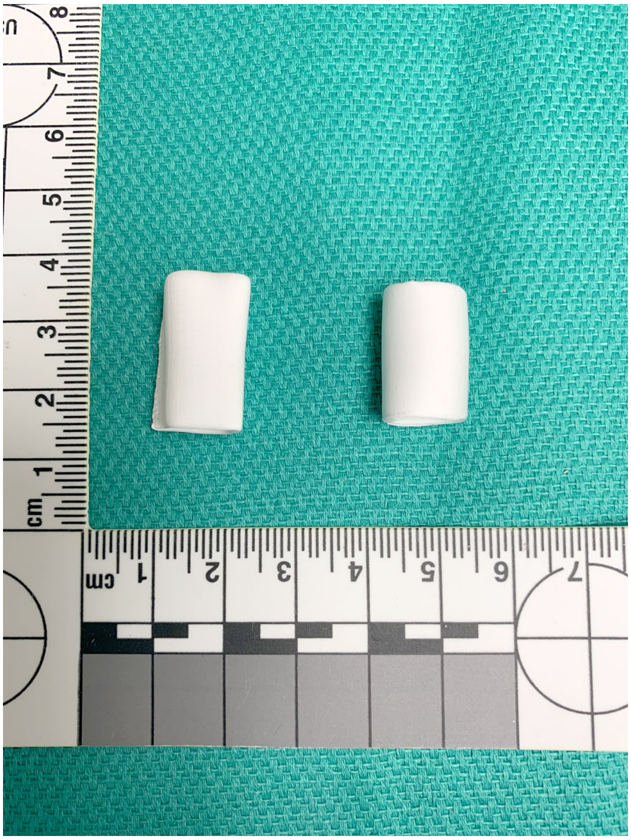

Figure 1. Presents a photo of the test and control conduits used in this study prior to implant. The graft on the left of the photo is the test conduit, with a diameter 10–11 mm at implant. The graft on the right is the control conduit, 10 mm in diameter at implant.

different time points in a growing lamb model. While the conduit is valve-less, its radially expansile properties and easy "stentability" allow for later insertion of a valved stent to provide pulmonary competence in the repaired, but dilating, right ventricle.

Materials and methods

Approval was obtained from the laboratory's Institutional Animal Care and Use Committee (IACUC).

Test conduit design

A 20 or 22 mm Stretch Gore-Tex^{TM} (ePTFE) graft was longitudinally cut and re-circularized using continuous 6-0 Gore-Tex^{TM} suture in a perpendicular direction such that the resultant diameter was 10–11 mm. The length of the test conduit was 2 cm for interposition (IP) implants. A representative photo of test and control devices is presented in Figure 1.

Experimental design

Experimental design is presented in Table 1. All lambs underwent interpositional implant of a Test (anisotropic) or Control (conventional PTFE) conduit within the main pulmonary artery (MPA). Demographic information for the lambs are presented in Table 2. Lambs in Group 1 (n = 8) were implanted and monitored with transthoracic echo (TTE) in the postoperative period. Lambs in Group 1 implanted with the Test conduit (n = 5) were balloon dilated at 3 months and 6 months post-implant with hemodynamic and angiographic assessment before and after each intervention. Hemodynamic and angiographic assessments were performed on animals in Group 1 implanted with the Control conduit (n = 3) concurrently with the test animals. Group 2 lambs (n = 6) had balloon dilation at 6 months post-conduit implant with angiography and hemodynamic assessment before and after balloon dilation. Following balloon dilation, Group 2a lambs (n = 3) were humanely euthanized, while Group 2b (n = 3) lambs were implanted with a self-expanding stent and recovered. Group 2b lambs underwent additional follow-up for another 3 months, at which point angiograms and hemodynamics were collected and the lambs were humanely euthanized. A comprehensive necropsy was performed on each animal at the end of the study.

Animals

Polypay lambs aged 8–12 weeks, weighing 15.3–23.0 kg were used for the study. Animals were fed Lamb Creep B90 (a ruminant diet), mixed with a sweet feed (may be medicated with lasalocid sodium 11.6 mg/lb), timothy hay cubes and loose hay. All animals were given water ad libitum throughout the study.

Fasting/preoperative preparation

Animals were fasted for 12–24 hours prior to anesthetic events with water provided ad lib. Sustained release (SR) Buprenorphine (SQ) was used for pre- and post- operative analgesia at a dose of 0.12–0.27 mg/kg, given in the 24 hours period prior to surgical induction.

Induction

Animals were sedated with 0.04 mg/kg atropine IM and 10 mg/kg ketamine IM. Supportive fluids, 0.9% normal saline (NaCl), were administered IV. Anesthesia was induced using 2–6 mg/kg Propofol IV. Animals were endotracheally intubated for mechanical ventilation at 10–15 breaths per minute, 4 LO_2/min, and 1–4% isoflurane. A stomach tube was inserted and approximately 1 pint of antacid was administered via the tube to prevent bloat. An antibiotic, 3 mg/kg ceftiofur IM, and corticosteroid, 250 mg methylprednisolone (or equivalent) IV, were administered prior to incision. The animal was positioned in the right decubitus position, aseptically prepped, and draped. Heart rate, respiratory rate, oxygen saturation, body temperature and intravenous fluid infusion rate were monitored.

Conduit implant

When the animal reached a deep plane of anesthesia, 0.4–0.8 mg/kg succinylcholine chloride was administered IV.

Table 1. Experimental design and data collection events.

Group	Device	N	Prior to Implant	Month 1 & 2	Month 3	Post-procedure	Month 4 & 5	Month 6
1	Test	5	BS	TTE	Angiograms Pressures Balloon expansion	BS	TTE	Angiograms Pressures Balloon expansion Euthanasia
	Control	3	BS	TTE	Angiograms Pressures	BS	TTE	Angiograms Pressures Euthanasia
			Prior to Implant	Months 1-5	Month 6	Post-procedure	Month 7 & 8	Month 9
2a	Test	3	BS	TTE	Angiograms Pressures Balloon expansion Euthanasia	NA	NA	NA
2b	Test	3	BS	TTE	Angiograms Pressures Balloon expansion Stenting	BS	TTE	Angiograms Pressures Euthanasia

BS = blood sample, TTE = transthoracic echocardiogram, NA = not applicable.

Table 2. Experimental animal demographic information.

Group	Weight (kg)	Age (days)
1 (Test)	18.4 ± 0.3	80 ± 3
1 (Control)	19.0 ± 2.5	85 ± 8
2 (Test)	16.5 ± 1.1	57 ± 5

A left thoracotomy was performed through the 4th intercostal space, the animal was heparinized (250 units/kg) and placed on single stage cardiopulmonary bypass. Conduit implant was performed on a beating heart during hypothermia. In both groups, the main pulmonary artery was isolated and cross clamped proximal to the pulmonary artery bifurcation.

A section of the MPA was excised to allow space for the conduit. The conduit was sewn interpositionally in place with a running stitch using 5-0 or 6-0 absorbable suture on each side of the conduit. For interpositional implantation of the anisotropic conduit directly to the RVOT, the MPA was transected 5–15 mm distal to the pulmonary valve. A longitudinal arteriotomy was subsequently made from the transected edge of the main PA, extending across the pulmonary annulus and into the RVOT (ventriculotomy) so that a 1.5–2 cm length of beveled conduit could be used for the proximal anastomosis. Once the conduit was implanted, mechanical ventilation recommenced and the animal was warmed to normothermia and weaned off cardiopulmonary bypass. When bypass cannulas were removed, heparin was reversed (Protamine, IV, approximate ratio of 10 mg protamine:1000IU of heparin). The thoracotomy was closed and animals were recovered from anesthesia.

Hemodynamic and angiographic assessment

Lambs were anesthetized to undergo hemodynamic and angiographic assessment at 3, 6 and/or 9 months post-conduit implant. The heart was catheterized for collection of intracardiac pressure data, angiograms, dimensional measurements, and for lambs implanted with the test conduit, balloon dilation and or stenting, dependent on experimental group. A modified Seldinger technique was used to insert a 12 Fr. introducer into the jugular vein. Intracardiac catheters (7 Fr. pigtail, 7 Fr. wedge pressure and 7 Fr. Swan-Ganz catheters) were inserted into the jugular vein introducer and advanced into the heart under fluoroscopic guidance. After collection of the data, lambs implanted with the test conduit underwent balloon dilation and/or stenting of the conduit. At the completion of the procedure, the introducer was removed and the vein repaired with 7-0 monofilament suture and the skin incision was closed in a normal fashion with 2-0 and 3-0 absorbable suture and animals were recovered from anesthesia. Buprenorphine (SQ) was used for pre- and post- operative analgesia at a dose of 0.12–0.27 mg/kg, given in the 24 hours period prior to surgical induction.

Balloon dilation of conduit

After collection of hemodynamic and angiographic data, a guidewire and guide catheter were introduced into the venous system and passed from the right atrium into the right ventricle. A 20 mm B. Braun Z-Med II™ valvuloplasty balloon catheter was advanced over the guidewire and positioned within the conduit. The balloon was inflated (1–2 dilations) to a pressure of 3–4 atmospheres. After completion, the balloon was removed and hemodynamic and angiographic assessments were performed again as described. For test lambs not receiving a stent, the introducer was removed and the vein repaired as described.

Balloon expansion of conduit with stent

For stent insertion, the test conduits were ballooned dilated as described above. A 20 mm Wallstent™ (Boston Scientific) delivery catheter was advanced over-the-wire and into the implanted conduit. Once in position, the stent was deployed within the conduit. Hemodynamics were measured post-stent insertion. When completed, the introducer catheter was removed and the vein repaired as described.

Table 3. Intracardiac pressures and diameters measured in Group 1 at 3 and 6 months post-implant.

3 months						
	Test (n = 5)		Control (n = 3)	p values		
Measurements	Pre-balloon dilation	Post-balloon dilation	Baseline	Pre-balloon vs. Control	Post-balloon vs. Control	Pre-balloon vs. Post-balloon
RV peak pressure (mmHg)	34.0 ± 16.0	26.0 ± 7.5	51.3 ± 11.0	0.005	0.004	NS
Trans-conduit gradient (mmHg)	18.0 ± 9.0	11.0 ± 6.0	37.0 ± 6.0	0.05	0.007	0.04
Conduit diameter (mm)	13.5 ± 2.5	15.2 ± 3.7	9.3 ± 1.3	0.005	<0.001	0.04
6 months						
	Test (n = 5)		Control (n = 3)	p values		
Measurements	Pre-balloon dilation	Post-balloon dilation	Baseline	Pre-balloon vs. Control	Post-balloon vs. Control	Pre-balloon vs. Post-balloon
RV peak pressure (mmHg)	34.8 ± 11.0	35.0 ± 8.0	61.0 ± 2.0	0.001	<0.001	NS
Trans-conduit gradient (mmHg)	11.6 ± 5.0	7.0 ± 3.0	47.0 ± 5.0	<0.0001	<0.001	NS
Conduit diameter (mm)	15.5 ± 1.9	16.8 ± 2.9	9.6 ± 0.4	<0.005	<0.001	0.02

NS = not significant.

Postoperative care

Animals were observed post operatively for normal recovery from surgery, appetite, fluid intake, voiding, ambulation, respiratory rate, respiratory effort, heart rate and rhythm, willingness to stand when approached, willingness to ambulate, development of ascites, and survival. Independent veterinary assessment was performed in the presence of atypical clinical appearance. After discharge from post-operative care, animals were housed long-term in a natural environment with pasture and appropriate shelter with on-site veterinary technical support.

Echocardiography

Transthoracic Echocardiography (TTE) exams were performed at 14 days after graft implant, and monthly throughout each animal's postoperative period. A comprehensive exam was performed following established guidelines [18].

Statistics

All data were collected using Microsoft Excel 2016, are expressed as means with standard deviations and analyzed by a paired t-test where appropriate. Statistical significance was defined as $p \leq 0.05$. Graft diameters were determined by taking the average of the diameters measured at the proximal, mid and distal points of the conduit.

Results

Experimental animal demographic information is summarized in Table 2. Control animals were slightly older and bigger compared to those implanted with test conduits in Groups 1 and 2 but the differences were not significant. The hemodynamics of lambs having balloon dilation and/or stenting of interposition conduits implanted in the MPA are summarized in Tables 3 and 4. Three months after the implantation, control animals showed significant increases in right ventricular pressures and trans-conduit gradients. In the anisotropic test group the RV pressure and trans-conduit gradient were significantly lower compared to controls (Table 3). The graft diameter was significantly larger in the test conduit group compared to controls due to spontaneous radial expansion of the conduit. Balloon dilation of anisotropic conduits at three months showed a reduction in RV pressure and significant improvement in the RV outflow tract gradient as well as significant increase in graft diameter, compared to both control and pre-dilation conditions (Table 3). At six months post implantation control animals continued to have significant elevation in RV systolic pressure and trans-conduit gradients. The RV systolic pressure, trans-conduit gradient and graft diameter did not significantly change from three months post implantation to six months post implantation in the anisotropic conduit group. Following balloon dilation at six months post implantation, the RV pressure and trans-conduit gradient were significantly lower than in controls (Table 3). Furthermore the graft diameter increased significantly compared to the pre-balloon and control conditions.

Table 4 summarizes angiographic findings and hemodynamics for stent insertion in anisotropic conduits. At 6 months post implantation test conduits had normal RV pressures that were significantly lower than in control animals (61.0 ± 2.0 mmHg vs. 27.6 ± 1.5 mmHg, $p < 0.001$), lower trans-conduit gradients (47.5 ± 5.0 mmHg vs. 13.1 ± 5.5 mmHg, $p < 0.001$), and significantly higher diameters (17.3 ± 1.2 mm vs. 9.6 ± 0.4 mm, $p < 0.001$). After balloon dilation and stenting of the anisotropic conduit, trans-conduit gradients decreased significantly (13.1 ± 5.5 mmHg pre vs. 4.3 ± 1.5 mmHg post, $p = 0.03$) and conduit diameters increased with a trend toward statistical significance (17.3 ± 1.2 mm pre vs. 18.7 ± 1.8 mm post, $p = 0.07$). Figure 2 presents angiograms and fluoroscopic images collected during a stent implant. Test animals in Group 2b were followed for an additional 3 months (i.e., 9 months post-implantation of conduit) and found to have continued radial expansion of the conduit, where the diameter increased to 19.9 ± 0.2 mm (vs 18.7 ± 1.8 mm at 6 months following balloon dilation, $p = 0.03$). The stented anisotropic conduit was further dilated at 9 months to 20.6 ± 0.8 mm, significantly larger than at the 6-month time-point ($p = 0.02$).

Table 4. Intracardiac pressures and diameters measured in Group 2 at 6 and 9 months post-implant.

6 months						
	Test A&B (n = 6)		Control (n = 3)	*p* values		
Measurements	Pre-balloon dilation	Post-balloon dilation	Baseline	Pre-balloon vs. Control	Post-balloon vs. Control	Pre-balloon vs. Post-Balloon
RV peak pressure (mmHg)	27.6 ± 1.5	26.0 ± 2.6	61.0 ± 2.0	<0.001	<0.001	NS
Trans-conduit gradient (mmHg)	13.1 ± 5.5	4.3 ± 1.5	47.0 ± 5.0	<0.001	<0.001	0.03
Conduit diameter (mm)	17.3 ± 1.2	18.7 ± 1.8	9.6 ± 0.4	<0.001	<0.001	0.07
9 months						
	Test B (n = 3)		Control (n= 3)[a]	*p* Values		
Measurements	Pre-balloon dilation	Post-balloon dilation	Baseline at 9 months	Pre-stent vs. Control	Post-stent vs. Control	Pre-stent vs. Post-stent
RV peak pressure (mmHg)	26.3 ± 3.5	28.0 ± 0.6	NA	NA	NA	NS
Trans-conduit gradient (mmHg)	7.0 ± 2.6	4.0 ± 3.0	NA	NA	NA	NS
Conduit diameter (mm)	19.9 ± 0.2	20.6 ± 0.8	NA	NA	NA	NS

NA = not applicable, NS = not significant.
[a]Control animals were not survived to 9 months, so comparison to Test animals cannot be performed.

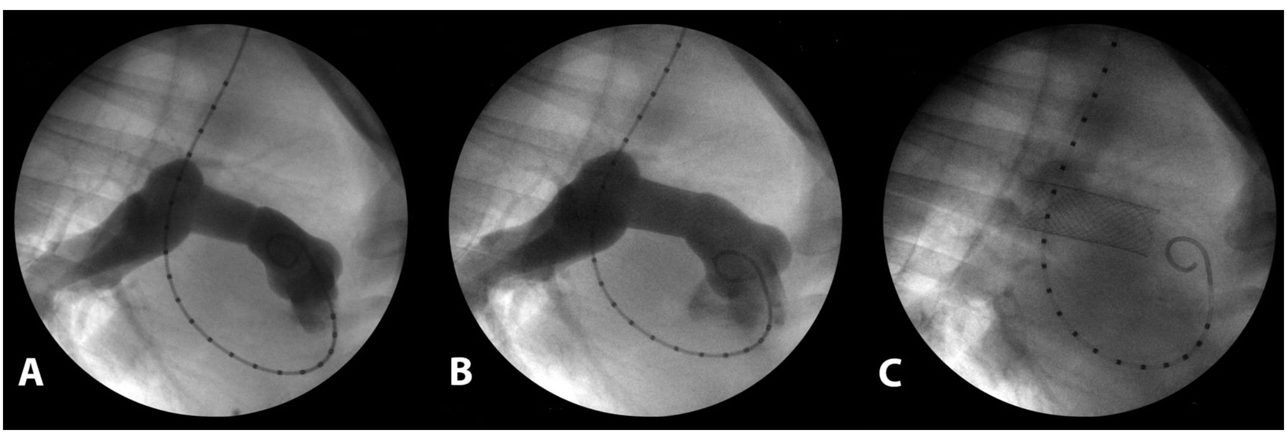

Figure 2. Presents angiograms and fluoroscopic images collected during stent implant within the test conduit at the 6 month time point. Image A is an angiogram of the implanted test conduit immediately following balloon dilation. Image B is an angiogram of the implanted stent within the test conduit. Image C is a fluoroscopic image of the implanted stent within the test conduit but without injected contrast filling the conduit and stent within.

Necropsy

Figure 3 shows gross pathology of conduits at different time points following balloon dilation and/or stenting. Figure 3A shows a specimen of an anisotropic conduit from Group 1. The conduit had a total length of 19 mm, with proximal, midpoint and distal diameters of 21.5 mm, 21.5 mm and 21 mm, respectively. The conduit was intact along its entire length, with no perforations nor tears, and was firm but easily flexible on manipulation. The proximal and distal anastomoses were well healed. The interior of the graft was smooth. There was no thrombus or vegetation, nor any hemorrhage noted in the tissue proximal to the graft. Anisotropic conduits explanted from lambs in Group 2a (balloon dilation at 6 months post-implantation, Figure 3B) also showed no evidence of tears, perforation, pseudoaneurysm, hemorrhage or clot deposition. The conduit was smooth throughout and the anastomoses well healed. Figure 3C,D show gross pathologic specimens of conduits explanted from lambs in Group 2b, (i.e., those having stent insertion at 6 months post-conduit implantation). The stent was firmly apposed to the arterial wall, without evidence of dissection, pseudoaneurysm, clot deposition or vegetation. There was no tissue ingrowth.

Discussion

The use of anisotropic ePTFE grafts as interposition conduits in the MPA results in spontaneous radial expansion of the conduit, favorable hemodynamics, and easy amenability to safe balloon dilation, with significant increases in graft diameter occurring after balloon dilation. We chose balloon dilation at two time points in growing lambs—3 months and 6 months post-implantation, and performed consecutive dilations at 3 and 6 months. The safest early balloon dilation is performed at 3 months because this is the time point that correlates best with usual clinical practice. It takes at least

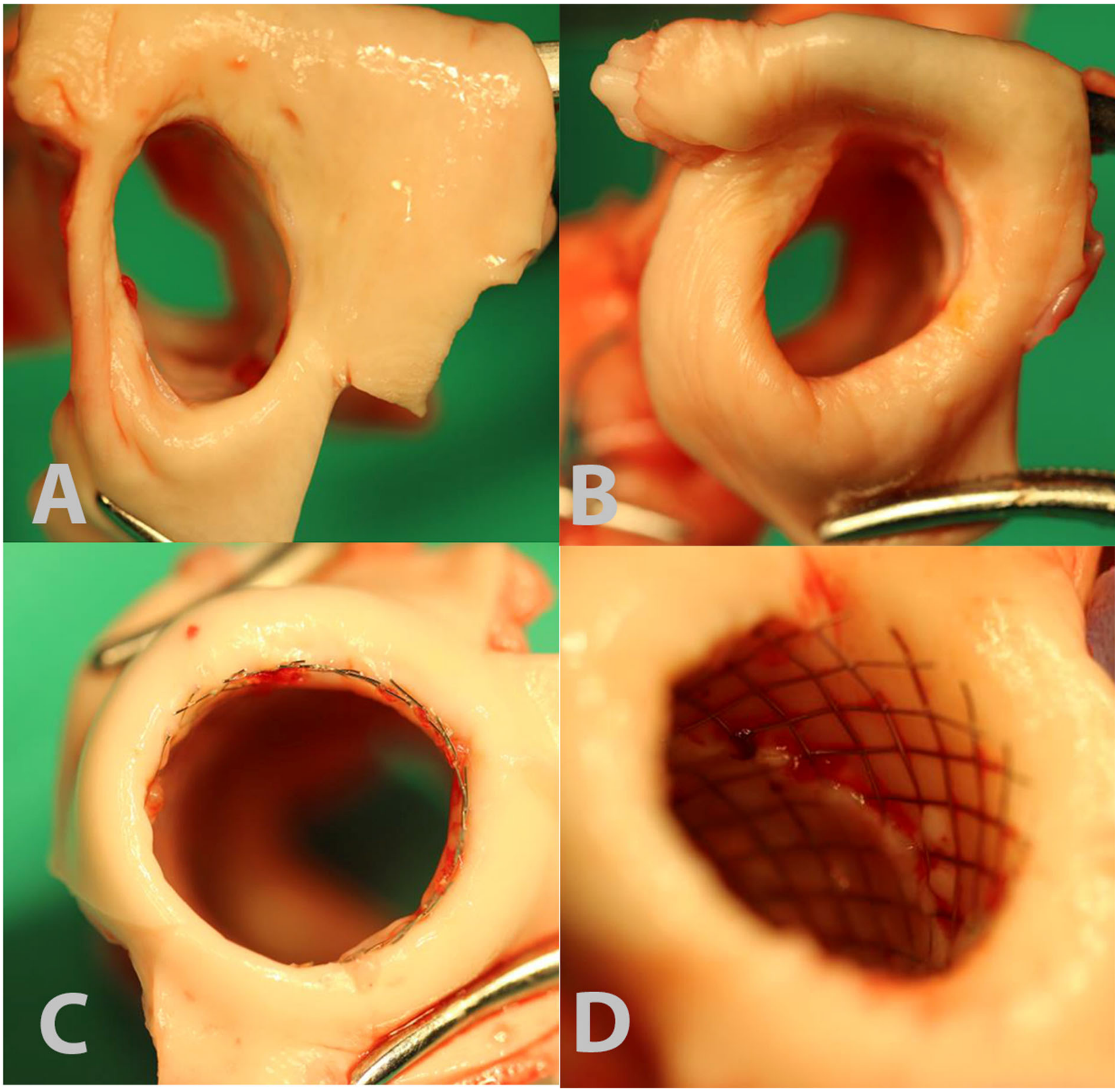

Figure 3. Presents gross pathology images of Test conduits following balloon dilation or stenting. Image A is a gross photograph of an explanted Test conduit from Group 1 at the six month time point, following balloon dilation at 3 and 6 months. Image B is a gross photograph of an explanted Test conduit from Group 2a following balloon dilation at 6 months. Images C and D are gross photographs of explanted Test conduits containing stents implanted in Group 2b. Images C and D were collected during necropsy at the 9 month time point.

8 weeks for anastomotic wound healing to reach 80–90% of maximal strength, so the 3-month time point was chosen for balloon dilation since it seems the earliest, safest time point that theoretically has adequate healing and a lower chance of rupture or dehiscence [19,20]. A 6 month balloon dilation is chosen because we believe that adequate healing has occurred by that time point, and this later dilation is necessary to show that the conduits are dilatable in a setting of a more mature scar formation around the conduit. Balloon dilation of the conduit at 3 months post implantation yields safe and effective results with increased radial expansion and reduction of trans-conduit gradients compared to controls, and no tears or pseudoaneurysm formation.

The increase in diameter and favorable hemodynamics of anisotropic conduits after being dilated at the 3 month post implantation time point is sustained at 6 months. There is no appreciable graft recoil, and in fact, there is continued slight radial expansion of the conduit. At 6 months post-implantation the conduit is safely re-dilatable and easily stented without tears, dissection, pseudoaneurysm, or clot formation. There is good healing at both proximal and distal anastomoses. The conduit also dilates effectively after 6 months of implantation, at a time with more scar deposition compared to 3 months.

The conduit showed expansion up to 20–22 mm in diameter across its entire length, supporting the notion that this conduit can reach adult dimensions with balloon dilation, is stentable, and can act as a landing zone for a valved stent for pulmonary competence, if necessary. Future studies include the safety and efficacy of the conduit as an RVOT conduit rather than an MPA interposition graft. We did not proceed to immediate evaluation of the conduit as an RVOT graft, because we wanted to illustrate the radial expansion properties of the conduit without any potential confounding effects from an anastomosis to the RV muscle.

Conclusions

Anisotropic conduits implanted as interposition grafts in the MPA show spontaneous expansion, can be safely and effectively dilated and/or stented at 3, 6, 9 months post-implantation. The conduit may accommodate the growth needs of children having cardiac surgical repair and can act as a landing zone for future insertion of a valved stent.

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Disclosure statement

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the article. The data that support the findings of this study are available from the corresponding author, JPC, upon reasonable request.

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