

Midterm performance of a novel restorative pulmonary valved conduit: preclinical results



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KEYWORDS

- bioresorbable scaffolds
- degenerative valve
- endogenous tissue restoration
- pulmonary stenosis
- transthoracic echocardiogram

Abstract

Aims: The Xeltis bioabsorbable pulmonary valved conduit (XPV), designed to guide functional restoration of patients' own tissue, is potentially more durable than current pulmonary bioprosthetic valves/valved conduits. The aim of this study was to assess the haemodynamic performance of the novel XPV implanted in an ovine model.

Methods and results: The XPV was surgically implanted in adult sheep under general anaesthesia and cardiopulmonary bypass (XPV group, n=20). Sheep that received a Hancock bioprosthetic pulmonary valved conduit served as a control group (HPV group, n=3). Transthoracic echocardiograms from VARC-2 recommended time points at 3, 6, 9, 12, 18 and 24 months (XPV group) and at 3 and 6 months (HPV group) after the procedure were analysed in an independent core laboratory. The primary endpoint was favourable valved conduit performance, defined as peak systolic pressure gradient <40 mmHg, no severe pulmonary regurgitation (PR), and a maximum conduit patency index of -20%. In the latter, negative values denote luminal narrowing and vice versa. The valvular peak systolic pressure gradient (mmHg) was 25.6±9.7 (3 months), 19.6±7.1 (6 months), 10.0±9.2 (24 months) in the XPV group and 18.4±6.6 (3 months), 17.7±4.6 (6 months) in the HPV group. The patency index (%) of the conduit at the valvular level was +30.3±13.6 (6 months) and +64.1±1.4 (24 months) in the XPV group and +2.0±15.9 (6 months) in the HPV group. PR was trace or mild at all visits, except in one animal with persistent moderate PR in the XPV group, up to 24 months.

Conclusions: The XPV showed a favourable and durable haemodynamic performance (up to two years after implantation), without conduit narrowing/obstruction or severe regurgitation.

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Abbreviations

ETR	Endogenous Tissue Restoration
HPV	Hancock pulmonary valved bioprosthesis
PA	pulmonary artery
PR	pulmonary regurgitation
RV	right ventricle
RVOT	right ventricular outflow tract
XPV	Xeltis pulmonary valved conduit

Introduction

Congenital defects involving the right ventricular outflow tract (RVOT) and the pulmonary artery (PA), such as tetralogy of Fallot, pulmonary atresia, or transposition of the great arteries with pulmonary stenosis, represent about 20-40% of patients with congenital heart disease who survive until adulthood^{1,2}. Reconstruction of the RVOT is part of the surgical repair of these conditions, and inevitably portends recurrent RVOT dysfunction requiring the implantation of a right ventricle (RV)-to-PA conduit or a prosthetic pulmonary valve. Unfortunately, the lifespan of these conduits is much shorter than the lifespan of the recipient patients because they degenerate, resulting in pulmonary regurgitation (PR), with resultant progressive RV dilation and failure³⁻⁶. In addition, these conduits do not allow for the natural growth of the child. In order to overcome these limitations, the development of more biocompatible conduits that have the potential to grow has been a challenging quest in recent years. The approaches to engineering a biocompatible pulmonary valve with growth potential typically involve the seeding of cells (endothelial cells, stem cells, amniotic fluid-derived cells, or autologous progenitor cells) to populate various scaffolds composed of biodegradable polymers, autologous tissue, or allograft or xenograft matrixes⁷⁻¹³. More recently, a new technology was developed based on a biodegradable

polymer matrix designed to enable Endogenous Tissue Restoration (ETR) without the use of stem cells or animal-derived products¹⁴. The novel polymeric valved conduit allows the patient's own cells to infiltrate and trigger a cascade of physiological events leading to gradual replacement of prosthetic material by native tissue. In this study, we sought to investigate the midterm performance of a novel biodegradable polymeric pulmonary valved conduit (XPV) in a sheep model.

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Methods

STUDY DESCRIPTION

The study included 23 adult Swifter sheep (age: two to four years, weight: 60-90 kg). The pulmonary valved conduit (Xeltis BV, Eindhoven, the Netherlands) was implanted in 20 sheep (XPV group) while the 22 mm Hancock[®] bioprosthetic valved conduit (Medtronic, Minneapolis, MN, USA), which consists of a porcine aortic valve sutured into the centre of a woven fabric conduit was implanted in three control sheep (HPV group). Two animals died early after implantation of the XPV because of arrhythmia and extensive clamping during the procedure. A third animal was sacrificed after five months due to infective endocarditis. Nine animals have no data available. Nine animals eventually constituted the XPV group available for follow-up. The study flow chart is shown in **Figure 1**.

The study protocol adhered to the Directive 2010/63/EU of the European Parliament and of the Council of 22 September 2010 on the protection of animals used for scientific purposes and the Guide for the Care and Use of Laboratory Animals and was reviewed and approved by the Test Facility's Ethical Committee for compliance with regulations prior to study initiation (EC approval no. EC MxCI 2014 - 027).

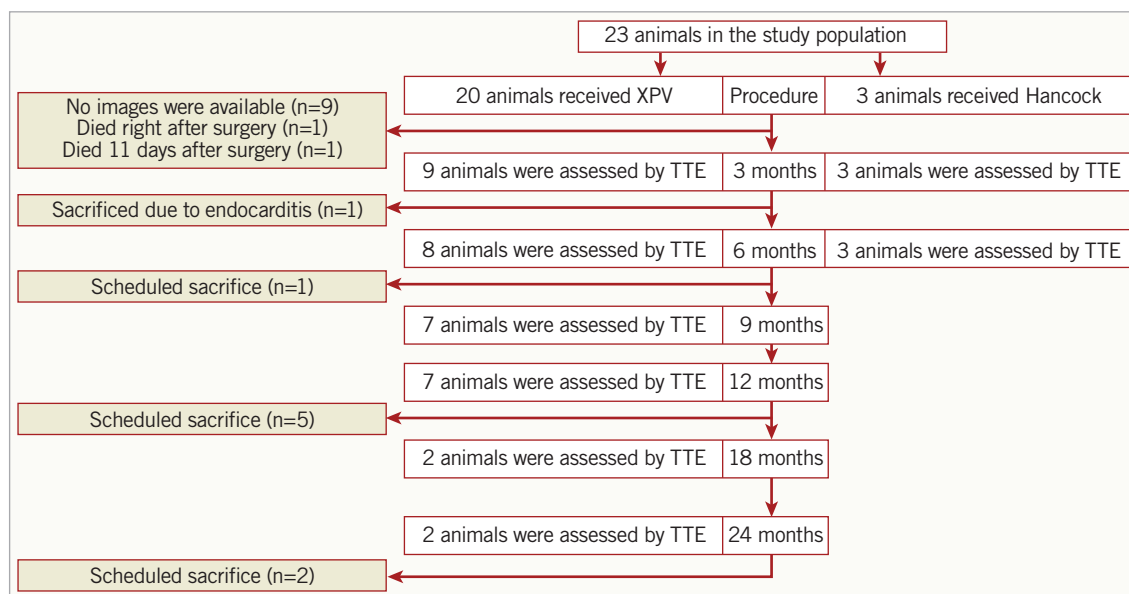


Figure 1. Flow chart of the study and the key echocardiographic assessment time points. TTE: transthoracic echocardiography

THE BIODEGRADABLE PULMONARY VALVED CONDUIT DESCRIPTION

The XPV is a flexible, highly porous conduit with three leaflets, fabricated by electrospinning from a novel supramolecular elastomer. The XPV has a length of 5 cm and an inner diameter of 21 mm. The concept of XPV is based on ETR, in which gradual restoration of the absorbable leaflet and conduit wall by the patient's own cells takes place. The leaflet and conduit are infiltrated by inflammatory cells, which release growth factors and promote smooth muscle cell infiltration and matrix (proteoglycans and collagen with focal elastic tissue) production, while the same inflammatory cells also ensure the absorption of the polymeric implants.

SURGICAL TECHNIQUE AND POSTOPERATIVE MANAGEMENT

The conduits (XPV 21 mm or HPV 22 mm) were surgically implanted under general anaesthesia and normothermic cardiopulmonary bypass on the beating heart. The heart was exposed by a left anterolateral thoracotomy through the third intercostal space. After transection of the native pulmonary artery, the graft was implanted as an interposition pulmonary artery vascular graft 0.5-1.0 cm above the native pulmonary valve, the leaflets of which had been surgically removed. The antithrombotic regimen consisted of enoxaparin (Clexane®; Sanofi Aventis, Diegem, Belgium) 20 mg twice daily and aspirin (Aspegic®; Sanofi Aventis) subcutaneous injection 250 mg for five days.

ECHOCARDIOGRAPHIC ACQUISITION

Echocardiographic acquisition was performed using a Vivid-I (GE Healthcare, Chicago, IL, USA) ultrasound machine in accordance with a pre-specified protocol in the Animal Test Facility (Medanex, Diest, Belgium). Transthoracic echocardiography (TTE) was performed on conscious animals at the following time points:

preoperative, one week after the procedure, every four weeks thereafter up to two years, and one week before animal sacrifice. Standard echocardiographic views were used to obtain two-dimensional (2D), spectral Doppler, and colour Doppler interrogation of the pulmonary valve, RVOT, and the main PA. For the assessment of the pulmonary valved conduit performance, echocardiographic acquisition included the following views: 2D images of the entire conduit as well as pulsed wave (PW) Doppler, continuous wave (CW) Doppler, and colour Doppler at the subvalvular, valvular, and distal conduit regions.

CORE LABORATORY ECHOCARDIOGRAPHIC ANALYSIS

As recommended by the Valve Academic Research Consortium (VARC)-2 guidelines, we chose mandated timelines for echocardiographic analysis¹⁵. Transthoracic echocardiograms at 3, 6, 9, 12, 18 and 24 months (XPV group) after implantation were analysed for XPV primary and secondary performance endpoints. Comparison between the XPV and HPV groups was performed at 3 and 6 months after the procedure.

All transthoracic echocardiograms were analysed in an independent core laboratory (Cardialysis, Rotterdam, the Netherlands) using the Image Arena version 4.6.3 workstation (TOMTEC, Munich, Germany). Measurements of Doppler velocities and 2D dimensions were performed in accordance with published guidelines¹⁶⁻¹⁹. **Figure 2** displays the locations at which the echocardiographic measurements of the conduit diameters and performance indices were performed.

CONDUIT FUNCTION

Haemodynamic assessments included peak velocity (m/sec) and mean and peak pressure gradients (mmHg) at the subvalvular and valvular levels of the conduit. Mean and peak pressure gradients were derived from PW or CW Doppler by manually tracing the spectral systolic velocity curves.

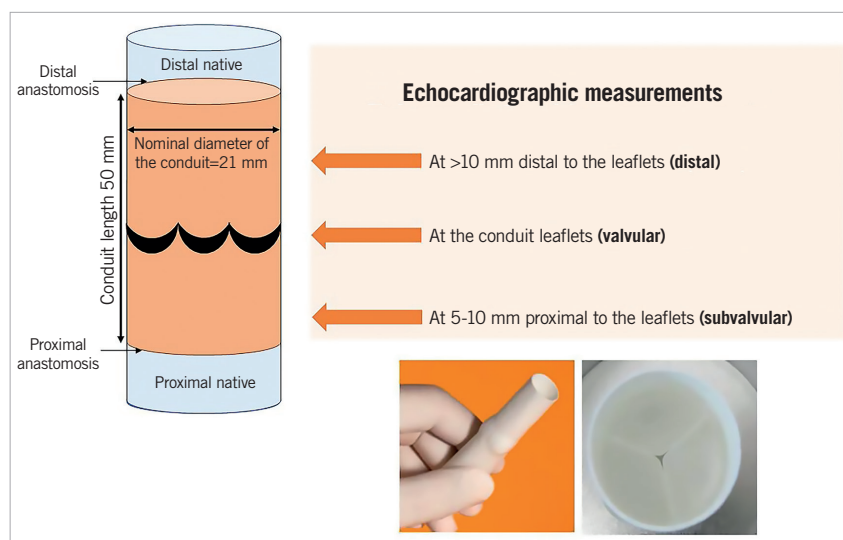


Figure 2. Diagram displaying the locations of echocardiographic measurements of the pulmonary valved conduit morphology and function.

Severity of pulmonary valve regurgitation (PR) was graded on a five-grade scale as none, trace, mild, moderate, or severe based on jet width criteria (**Table 1**) and/or colour Doppler flow reversal criteria (**Table 2**)²⁰. Clinically relevant PR was defined as at least mild PR.

Table 1. Jet width criteria of pulmonary regurgitation severity.

Grade	Description
None	No diastolic colour flow jet
Trace	Pinhole colour flow jet on ventricular side of the leaflets
Mild	Jet width <20% of the valve/conduit width*
Moderate	Jet width 20% to 40% of the valve/conduit width
Severe	Jet width >40% of the valve/conduit width

*As measured at the valvular (leaflet) level.

Table 2. Flow reversal criteria of pulmonary regurgitation severity.

Grade	Description
None	No diastolic colour flow reversal at level of the valve leaflets
Trace	Diastolic colour flow reversal beginning at the valve leaflets
Mild	Diastolic colour flow reversal extending above the valve leaflets but confined to proximal half of main PA
Moderate	Diastolic colour flow reversal extending into distal main PA
Severe	Diastolic colour flow reversal extending into PA branches

PA: pulmonary artery

CONDUIT MORPHOLOGY

Measurements of the conduit diameter at early to mid-systole were intended at the level of the conduit leaflets (valvular), 5-10 mm proximal to the leaflets (subvalvular), and >10 mm distal to the leaflets (distal).

The conduit patency index (CPI) was calculated to assess narrowing or expansion of the conduit at the subvalvular and valvular levels from three months post implantation to a given follow-up time point ($=[\text{conduit diameter at follow-up} - \text{conduit diameter at}$

3 months]/conduit diameter at 3 months%). A negative CPI value suggests conduit narrowing due to, e.g., neointimal hyperplasia, and a positive CPI suggests conduit expansion.

The primary endpoint of the study was the XPV performance at postoperative 3, 6, 9, 12, 18 and 24 months. A favourable performance of the XPV was defined as freedom from all of the following: 1) a transvalvular peak systolic pressure gradient >40 mmHg, 2) conduit narrowing as demonstrated by a reduction of the CPI of 20% or more, and 3) severe PR.

STATISTICS

Continuous variables with normal distribution were expressed as mean±SD, while continuous variables with non-normal distribution were expressed as median and interquartile range (IQR). No formal statistics were performed in this study due to the small sample size and the exploratory nature of the study.

Results

As shown in **Table 1**, all echocardiographic parameters were measurable in the majority of cases (88-100%), except for the distal conduit diameter, which could be reliably measured in only one third of cases. Therefore, measurements at the subvalvular and valvular conduit levels are reported in the results.

STUDY PRIMARY ENDPOINT (Table 3)

A favourable valve haemodynamic performance was achieved in all study animals. The average peak systolic pressure gradient (PG) at the valvular level was 25.6±9.7 mmHg (3 months), 10.0±9.2 mmHg (24 months) in the XPV group and was 18.4±6.6 mmHg (3 months), 17.7±4.6 mmHg (6 months) in the HPV group. Except for a single case that showed a temporary rise of peak PG >40 mmHg at the three-month evaluation, all other cases did not show a significant rise (>40 mmHg) at any time point and tended to decline over time (**Figure 3**). Therefore, although they tended to be higher early post procedure, peak PG values were eventually lower in the XPV group at the end of follow-up than in the HPV group at 3 and 6 months (**Table 3**).

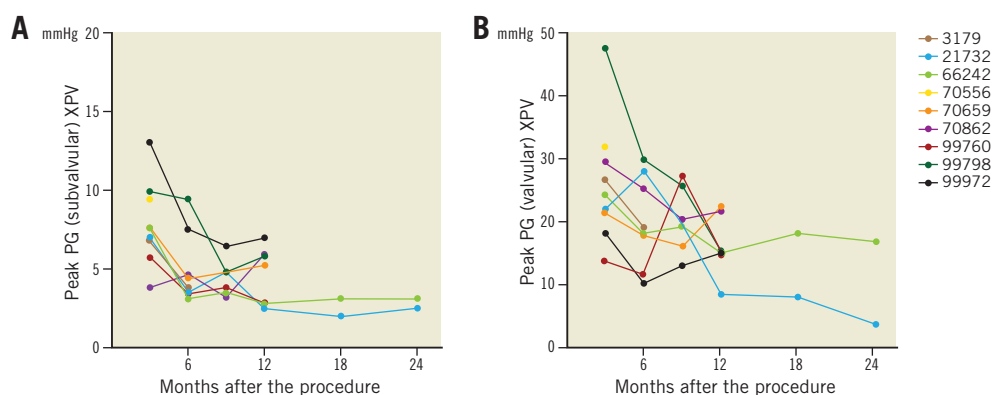


Figure 3. Serial changes of peak pressure gradient of individual animals at the subvalvular (A) and valvular (B) levels of the biodegradable pulmonary valved conduit.

Table 3. Summary of quantitative echocardiographic assessments.

	Visit	3 months	6 months	9 months	12 months	18 months	24 months
Device used (number)							
	XPV	9	8	7	7	2	2
	HPV	3	3				
Maximal conduit dimensions (mm)							
Subvalvular	XPV	18.7±2.0	23.5±2.0*	25.2±2.6	27.2±2.8*	24.9±0.1	24.6±0.2
	HPV	18.6±1.3	19.5±1.7				
Valvular	XPV	18.4±2.4	23.8±3.0*	26.5±3.3*	27.1±2.0 [#]	26.0±0.8	25.8±1.3
	HPV	18.4±1.2	18.7±1.9				
Conduit patency index (%)							
Subvalvular	XPV	NA	27.6±9.8*	38.3±11.2	48.2±10.1*	52.7±8.0	50.8±6.1
	HPV	NA	5.7±16.3				
Valvular	XPV	NA	30.3±13.6*	47.8±12.1*	48.6±15.0 [#]	65.2±4.5	64.1±1.4
	HPV	NA	2.0±15.9				
Pulmonary regurgitation (jet width to RVOT ratio, %)							
	XPV	12.9±4.9	15.7±8.3	16.6±13.5	15.1±8.1	18.4±15.8	20.0±11.3
	HPV	7.2±3.1 [†]	6.3±0.3				
Mean systolic pressure gradient (mmHg)							
Subvalvular	XPV	4.3±1.6	2.7±1.2	2.5±0.7	2.5±1.1	1.4±0.3	1.4±0.4
	HPV	3.0±0.9	3.6±1.5				
Valvular	XPV	15.1±6.5	10.9±3.9	10.6±3.1	8.2±3.3	6.2±2.4	5.4±4.7
	HPV	10.6±3.6	9.7±2.0				
Peak systolic pressure gradient (mmHg)							
Subvalvular	XPV	7.9±2.7	5.0±2.3	4.5±1.1	4.6±1.8	2.6±0.8	2.8±0.4
	HPV	5.4±1.6	6.9±2.4				
Valvular	XPV	25.6±9.7	19.6±7.1	19.7±4.9	15.8±4.7	12.8±7.1	10.0±9.2
	HPV	18.4±6.6	17.7±4.6				
Peak flow velocity (m/s)							
Subvalvular	XPV	1.4±0.2	1.1±0.2	1.1±0.1	1.0±0.2	0.8±0.1	0.8±0.1
	HPV	1.2±0.2	1.3±0.2				
Valvular	XPV	2.5±0.5	2.2±0.4	2.2±0.3	2.0±0.3	1.8±0.5	1.5±0.8
	HPV	2.1±0.4	2.1±0.3				
Heart rate (bpm)							
	XPV	121±14	113±25	126±23	127±22	113±18	81±6
	HPV	146±18	113±8				

*n=6; [#]n=5; [†]n=2. HPV: Hancock pulmonary valved conduit; NA: not available or not applicable; RVOT: right ventricular outflow tract; XPV: Xeltis biodegradable pulmonary valved conduit

The CPI (%) in the XPV group was +27.6±9.8 at six months and +50.8±6.1 at 24 months post procedure at the subvalvular level, while it was +30.3±13.6 at six months and +64.1±1.4 at 24 months at the valvular level. At six months, the CPI in the HPV group was +2.0±15.9 at valvular level and +5.7±16.3 at subvalvular level (Table 3). None of the animals in the XPV group had a narrowing >20% across the conduit at any time point (Figure 4).

PR severity was trace or mild at all follow-up time points in eight animals and consistently moderate in one animal in the XPV group, while PR was trace in the HPV group animals up to six months (Table 4, Figure 5). In the XPV group, the PR jet width to

RVOT ratio was <20% in five animals and >20% in two animals 12 months after implantation. According to the flow reversal criteria, PR severity was trace or mild in six animals and moderate in one animal 12 months after procedure in the XPV group. There was a discrepancy of the PR severity between jet width criteria and flow reversal criteria in a single animal, in which PR was eventually adjudicated as mild.

OTHER STUDY ENDPOINTS

Other parameters of valve performance were examined in the XPV group at 12 and at 24 months after the procedure and compared to the

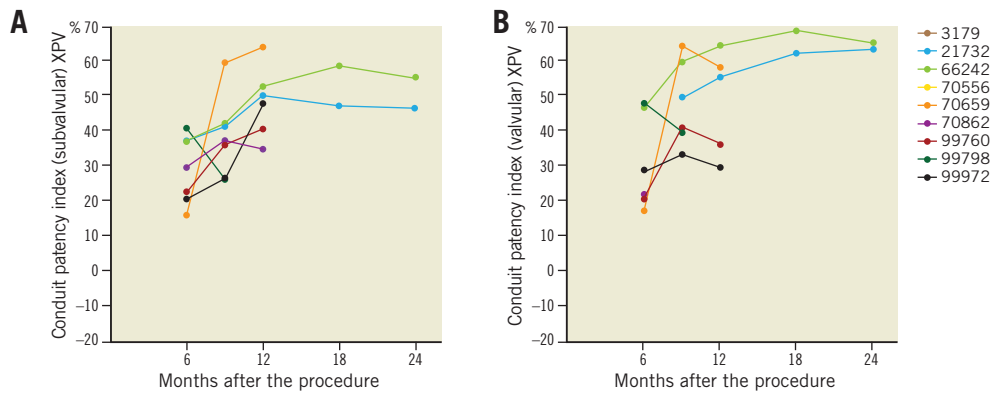


Figure 4. Serial changes of the conduit patency index of individual animals at the subvalvular (A) and valvular (B) levels of the Xeltis biodegradable pulmonary valved conduit.

Table 4. The severity of pulmonary regurgitation for sheep in the two study groups.

Animal ID	Device	3 months	6 months	9 months	12 months	18 months	24 months
3179	XPV	Mild	Mild	NA	NA	NA	NA
21732	XPV	Mild	Trace	Trace	Trace	Trace	Trace
66242	XPV	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate
70556	XPV	Mild	NA	NA	NA	NA	NA
70659	XPV	Mild	Mild	Trace	Mild	NA	NA
70862	XPV	Mild	Mild	Mild	Mild	NA	NA
99760	XPV	Trace	Mild	Mild	Mild	NA	NA
99798	XPV	Mild	Mild	Mild	Mild	NA	NA
99972	XPV	Mild	Mild	Trace	Trace	NA	NA
21079	HPV	Mild	Mild	NA	NA	NA	NA
70215	HPV	NA	Mild	NA	NA	NA	NA
71256	HPV	Mild	Mild	NA	NA	NA	NA

HPV: Hancock pulmonary valved conduit; XPV: Xeltis pulmonary valved conduit

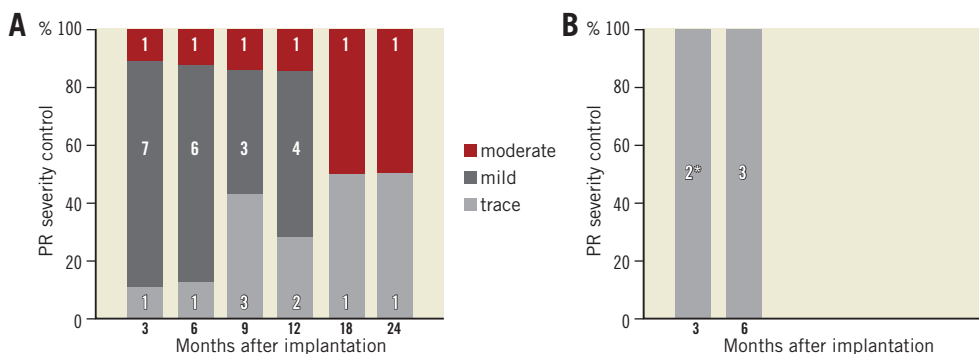


Figure 5. The severity of pulmonary regurgitation at different time points after implantation of the biodegradable pulmonary valved conduit (A) and the Hancock valved conduit (B). The number of subjects remaining at each time point, for each severity, is shown in the bars. *Animal #70215 images were non-analysable.

respective measurements performed at 3 and 6 months in the HPV group. Mean systolic PG at the valvular level was 15.1 ± 6.5 mmHg (3 months), 10.9 ± 3.9 (6 months) and 5.4 ± 4.7 mmHg (24 months) in the XPV group and was 10.6 ± 3.6 mmHg (3 months) and 9.7 ± 2.0 mmHg (6 months) in the HPV group. Mean systolic PG was <20 mmHg in all XPV group animals at both the subvalvular and

the valvular levels of the conduit 12 months ($n=7$) and 24 months ($n=2$) after the procedure. Mean systolic PG decreased over time in the XPV group while it did not change in the HPV group between 3 and 6 months after implantation (Figure 6).

None of the animals in the XPV group had a peak velocity >3 m/s at subvalvular or valvular levels of the conduit 12 and

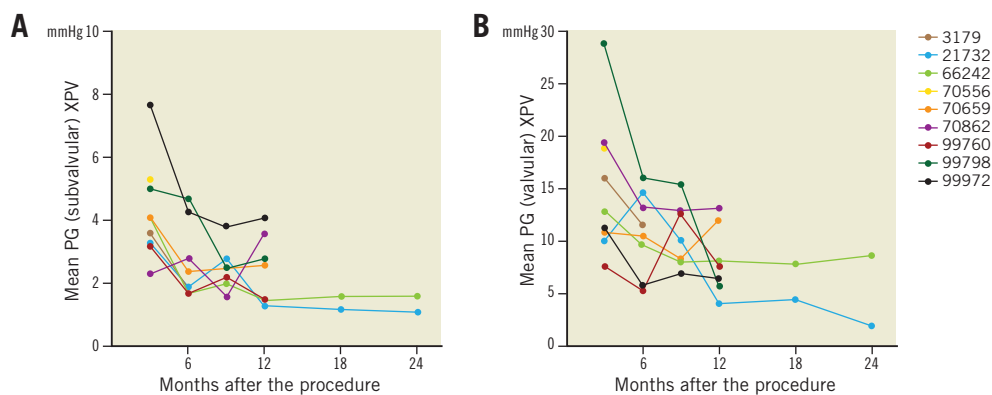


Figure 6. Serial changes of mean pressure gradient of individual animals at the subvalvular (A) and valvular (B) levels of the biodegradable pulmonary valved conduit.

24 months after the procedure (n=7). Although one animal had a peak velocity >3 m/s at the valvular level 3 months after the procedure, the peak velocity at 6 months decreased to <3 m/s. Peak velocity decreased over time in the XPV group (**Figure 7, Table 3**), while peak velocity in the HPV group did not change between 3 and 6 months (**Table 3**).

The subvalvular conduit diameter of XPV increased from 18.7 ± 2.0 at 3 months to 27.2 ± 2.8 and 24.6 ± 0.2 at 12 and 24 months, respectively. In contrast, the subvalvular conduit diameter in the HPV group was 18.6 ± 1.3 and 19.5 ± 1.7 at 3 and 6 months, respectively. Similarly, the valvular conduit diameter of XPV increased from 18.4 ± 2.4 at 3 months to 27.1 ± 2.0 and 25.8 ± 1.3 at 12 and 24 months, respectively, while in the HPV group it was 18.4 ± 1.2 vs. 18.7 ± 1.9 at 3 and 6 months, respectively (**Figure 8, Table 3**).

Discussion

In 20-40% of adults with congenital heart disease, there is an RVOT abnormality requiring implantation of an artificial conduit between the RV and the PA¹². Regardless of the technique used to reconstruct the RVOT, conduit dysfunction is common, and freedom from degeneration at 10 years is 51% in the case of

homografts implanted before the age of 10 years⁵. Accordingly, many patients have their third RVOT intervention by the age of 20 years²¹. Reintervention is associated with discomfort, disfigurement, cost, morbidity, and mortality.

The XPV is a next-generation conduit fabricated from a novel supramolecular elastomer that enables endogenous cells to populate the scaffold and to produce matrix. In the present study, echocardiographic analysis by an independent core laboratory showed a favourable haemodynamic performance as well as an acceptable regurgitation severity of the XPV, sustained up to two years after implantation. Morphologically, the XPV showed no narrowing or abnormal growth during the follow-up period. The definition of a favourable valve haemodynamic performance in this report was based on the best clinical judgement, published data on established pulmonary prosthetic valves/conduits, and practice guidelines^{19,22,23}.

In two animals, haemodynamic findings warrant more discussion. Animal #99798 initially had a high peak systolic PG at the valvular level at three months, which was consistently improving on later echocardiograms, eventually approaching acceptable values. The peak transvalvular gradient decreased to <30 mmHg at six months and to <20 mmHg on the 12-month echocardiogram.

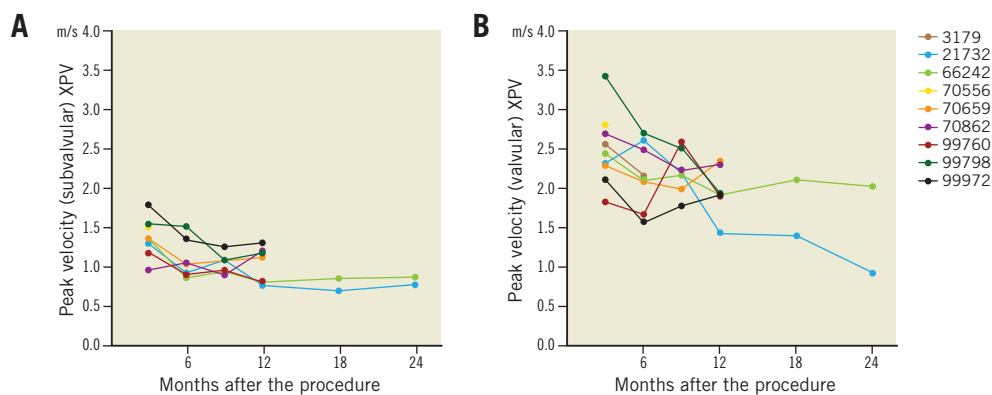


Figure 7. Serial changes of peak velocity of individual animals at the subvalvular (A) and valvular (B) levels of the biodegradable pulmonary valved conduit.

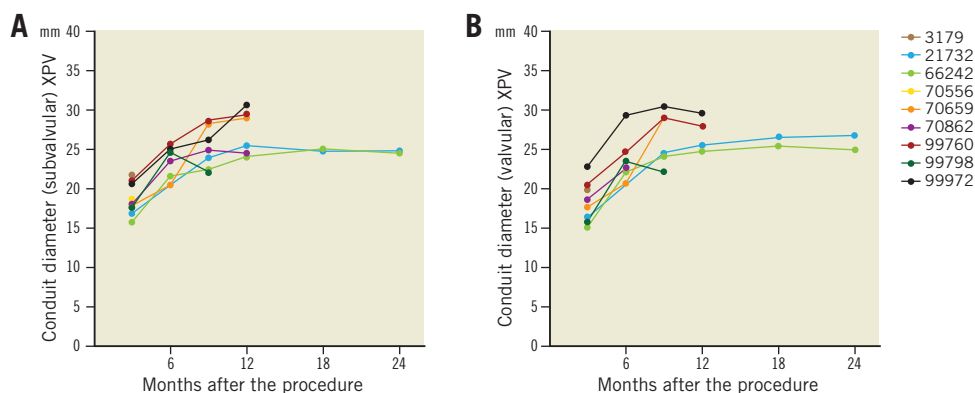


Figure 8. Serial changes of conduit diameter of individual animals at the subvalvular (A) and valvular (B) levels of the biodegradable pulmonary valved conduit.

There are no clear echocardiographic findings, or other clinical ones, to explain this temporarily high PG. However, a transient thrombus is a likely explanation.

Moderate PR was consistently seen in animal #66242 up to 24 months after the procedure. This animal showed a CPI of up to +70%, denoting a considerable increase in the conduit diameter during follow-up, ranking highest among all the animals in terms of luminal expansion. On the other hand, the actual diameter of the XPV in that animal (#66242) was 25 mm, which is the same diameter as another animal (#21732) at the latest follow-up at 24 months. These values are, in fact, only 4 mm larger than the nominal implantation diameter of 21 mm. Likewise, another animal (#99972) with even more increased diameter at 12-month follow-up had only trace PR.

There are limited data on precise echo Doppler cut-off values to define prosthetic pulmonary valve dysfunction. The American Society of Echocardiography guidelines recommend using RV-to-PA peak velocity as well as peak and mean PG for the evaluation of prosthetic pulmonary valve function. The normal performance of a pulmonary prosthetic valve is defined by a peak transprosthetic velocity of <3.2 m/s and a mean transprosthetic pressure gradient <20 mmHg¹⁸. In the Melody Transcatheter Pulmonary Valve Post-Approval Study (NCT01186692), a mean pressure gradient of ≤30 mmHg and PR <moderate at six months were used as the intended transcatheter valve performance criteria²⁴. Procedural success was defined as a transcatheter pulmonary valve implanted in the desired location, and RV-PA peak gradient <35 mmHg (derived from invasive measurement), no more than mild PR on angiography, and freedom from explantation at 24 hours post implantation²⁴. Structural valve deterioration of the surgically implanted Freestyle™ bioprosthetic valve (Medtronic) was defined as a composite of significant stenosis (a peak transvalvular gradient of >50 mmHg or a mean transvalvular gradient of >35 mmHg), or significant regurgitation (moderate or greater) on echocardiography²⁵.

In line with the haemodynamic data of established transcatheter and surgical pulmonary valve prostheses as well as the Hancock 22 mm conduit used in this study, the XPV has favourable

haemodynamic data. These data are to be confirmed in a human clinical study, which is currently underway.

Limitations

Interpretation of this study is limited by the relatively small number of echocardiographic evaluations available. Echocardiograms at the immediate postoperative time point (t=0) were not available. Absence of a clear electrocardiographic signal on echocardiographic images was another limitation, particularly for PR assessment. Ideally, the conduit dimensions should be quantified on a three-dimensional imaging modality.

Conclusions

The XPV shows encouraging results in an adult sheep model up to 24 months after implantation without luminal narrowing or haemodynamic deterioration.

Impact on daily practice

The use of biodegradable valves and conduits, such as the Xeltis pulmonary valved conduit endogenous tissue restorative technology would minimise or even eliminate the complications related to the use of prosthetic materials. Patients would have fewer thrombotic or degenerative prosthetic valves, thus less need for antithrombotic use as well as less need for reintervention. Another important aspect of this novel endogenous restorative technology is that it allows growth of the implanted material. The latter is essential in treating children with congenital heart disease. This study suggests that haemodynamic performance of a novel pulmonary valved conduit is favourable up to two years after implantation in a preclinical setting.

Guest Editor

This paper was guest edited by Alec Vahanian, MD, PhD; Department of Cardiology, Hôpital Bichat, Paris, and University Paris VII, Paris, France.

Conflict of interest statement

M. Brugmans and M. Cox are employed by Xeltis. P.W.Serruys is part of the Scientific Advisory Board of Xeltis. The other authors have no conflicts of interest to declare. The Guest Editor is a consultant for Edwards Lifesciences.

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