Pulmonary Valve Replacement: A New Paradigm with Tissue Engineering

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Abstract: Prevalence of congenital heart diseases worldwide is around 9 per 1000 newborns, 20% of which affect the pulmonary valve or right ventricular outflow tract. As survival after surgical repair of these defects has improved over time, there is the need to address the long-term issues of older children and young adults with "repaired" congenital heart diseases. In recent decades, the most used types of valves are the mechanical and bioprosthetic valves. Despite improving patients' quality of life, these effects are suboptimal due to their limitations, such as the inability to grow and adapt to hemodynamic changes. These issues have led to the search for living valve solutions through tissue engineering to respond to these challenges. This article aims to review the performance of traditional pulmonary valves and understand how tissue engineering-based valves can improve the management of these patients. (Curr Probl Cardiol 2023;48:101212.)

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Introduction

Pulmonary valve replacement (PVR) is required in different situations such as isolated pulmonary valve diseases, pulmonary valve defects due to congenital heart diseases (CHD) like tetralogy of Fallot (ToF) or any congenital disease repaired with a right ventricle-to-pulmonary artery conduit.[1,2]

Nowadays the prevalence of CHD worldwide is around 9 per 1000 newborns.[1] Approximately 20% of newborns with CHD have malformations of the pulmonary valve or right ventricular outflow tract (RVOT).[3]

As survival after surgical repair of congenital heart defects has improved over the last decades, there is the need to address the long-term issues of older children and young adults with "repaired" congenital heart disease.[2,4] The proportion of children that reaches adulthood is mainly determined by early surgery mortality, which is currently between 0% and 2%.[5] Half of patients who survive to ToF repair require PVR within 30 years.[4] As a result, PVR or RVOT reconstruction is becoming the most frequent congenital heart surgical procedure performed on adolescents and young adults.[2]

In recent decades, the most used types of valves are the mechanical and bioprosthetic valves. Despite improving patients' quality of life, these effects are suboptimal due to their limitations, such as the inability to grow and adapt to hemodynamic changes. These issues have led to the search for living valve solutions through tissue engineering to respond to these challenges.[6]

In this article we review the performance of traditional valves in situations that require PVR (eg, ToF, pulmonary stenosis or Ross procedure), paying special attention to its performance in younger patients. Also, we aim to understand how tissue engineering-based valves can help to overcome limitations that traditional valves have and if they will be able to improve the management of CHD that require PVR.

Methods

Research was performed on PubMed/MEDLINE, ScienceDirect, Scopus, and ResearchGate databases to identify the most recent articles to review the different type of valves used for pulmonary valve replacement nowadays. The following search terms were used: Pulmonary valve replacement, right ventricular outflow tract reconstruction, pulmonary allograft, bioprosthetic pulmonary valve, mechanical pulmonary valve, expanded polytetrafluoroethylene (ePTFE) pulmonary valve, bovine jugular veins conduit, tissue engineered pulmonary valve. Also we searched

in ClinicalTrials.gov to evaluate the latest outcomes of tissue engineered pulmonary valves in clinical trials, using the following search terms: Pulmonary valve replacement, tissue engineered pulmonary valve, tissue engineered heart valve in pulmonary position.

Results

Primary Disease

Regarding pulmonary valve diseases, they are mostly congenital and are often associated with CHDs. These conditions may lead to hemodynamic disturbances and the requirement for surgical procedures on the pulmonary valve. This usually leave the valve slightly stenotic or insufficient, requiring regular follow-up or even a future intervention.[7]

Tetralogy of Fallot. ToF is responsible for about 10% of all CHD with a prevalence of 1 per 3500 to 1 per 4300 in adult population.[8] It usually causes 4 heart defects: ventricular septal defect, an overriding aorta, right ventricular (RV) hypertrophy and right ventricular outflow tract obstruction (RVOTO). RVOTO determines the patient's clinical course; for example, people with minimal obstructions will experience physiological signs such as mild cyanosis, while those with severe obstruction have severe cyanosis and require short-term intervention. Approximately 80% of patients with ToF will have some degree of pulmonary stenosis and 20% will have pulmonary atresia[9].

Treatment of patients with ToF typically is based on correction of the ventricular septum and RVOTO release in the first 6 months of life.[9]

After the RVOTO release surgery some progressive dysfunction of the right ventricular outflow tract remains, leading to pulmonary valve insufficiency. After 5-10 years of the repair, between 40% and 85% of patients will have moderate to severe pulmonary regurgitation (PR).[10,11]

It is considered that the timely restoration of pulmonary valve competence may interrupt the progressive adverse remodeling of the RV. Thirty-five years after the treatment of ToF, PVR will have occurred in 40% of patients. As more patients with ToF survive, the number of PVRs performed has been increasing.[10,12]

Pulmonary Stenosis. It is the most common cause of RVOTO. Isolated PS occurs in 8%-10% of CHD but it is usually associated with other congenital diseases. Indeed, the most cases of severe PS is resolved in childhood by a percutaneous balloon valvuloplasty so, cases that require

surgery in adulthood are extremely rare.[13] However, for patients who are not eligible for or failed percutaneous intervention, surgical treatment is required. At operation, the valve usually cannot be repaired, so PVR is performed.[12,14]

Pulmonary Regurgitation. PR is usually caused by prior interventions on the pulmonary valve, such as percutaneous and surgical interventions or also, can be a part of more complex diseases like ToF.[7,13] PR in anatomically normal pulmonary valves can be caused by pulmonary hypertension or dilated pulmonary artery in Marfan syndrome.[13]

At the beginning PR is well tolerated, but a severe regurgitation within several years leads to right ventricular dilation and dysfunction together with development of tricuspid regurgitation. PVR is indicated in such cases and should not be delayed to prevent right ventricular failure.[12,14]

Ross Procedure. One more significant situation that may lead to PVR is the Ross procedure in which a diseased aortic valve is replaced with the patient's own pulmonary valve followed by the replacement of the pulmonary valve with a pulmonary allograft.[15] This procedure is a very viable option for children that require an aortic valve replacement since, unlike a prosthetic valve, it fits in a smaller size and will keep growing as the child grows.[16] It has an excellent hemodynamic profile and the risk of embolic complications is almost null. Thus, it is not necessary to take oral anticoagulants for life. The Ross procedure also has some limitations since the pulmonary homograft will develop regurgitation or stenosis after 15-20 years, requiring another procedure.[17]

Indications for Pulmonary Valve Replacement

It is important to take a look at the most recent 2020 ESC guidelines and 2018 American College of Cardiology/American Heart Association Guideline for the Management of Adults with Congenital Heart Disease to understand when PVR will be required to treat consequences of CHD. Indications for intervention in severe RVOTO and after ToF repair are summarized in Tables 1 and 2.

In patients with pulmonary regurgitation after the repair of isolated pulmonary stenosis, PVR is recommended in symptomatic patients with moderate or greater PR with RV dilatation or dysfunction (class I). If the patient is asymptomatic, but also has moderate or greater PR with progressive RV dilatation or dysfunction, PVR should be considered (class IIa).[12]

TABLE 1. Recommendations for intervention in severe RVOTO

Provided that PVR is not required	RVOTO intervention is recommended at any level regardless of symptoms
Provided that PVR is required	PVR is indicated in symptomatic patients In asymptomatic patients PVR is indicated in the presence of 1 or more of the following: - Clear decrease in exercise capacity - Decreasing RV function and/or progression of tricuspid regurgitation to at least moderate - Right ventricular systolic pressure (RVSP) > 80 mmHg - Right-to-left shunting via an arterial septal defect or ventricular septal defect

PVR, pulmonary valve replacement; RV, right ventricle; RVOTO, right ventricular outflow tract obstruction; RVSP, right ventricular systolic pressure.

Pulmonary Valve Replacement Options

To treat the conditions described above, PVR is the upfront treatment in most cases. There is not a single valve that is considered the best for all patients and, therefore, the choice must be individualized, taking into account primary diagnosis, RVOT anatomy, age and size of the patient, previous surgical history and patient choice.[7]

TABLE 2. Recommendations for intervention after repair of tetralogy of Fallot

- PVR is recommended in symptomatic patients with severe PR and/or at least moderate RVOTO (class I)
- PVR should be considered in asymptomatic patients with severe PR and/or RVOTO when one of the following criteria is present: (class IIa)
  - Decrease in objective exercise capacity
  - Progressive RV dilation to right ventricular end systolic volume indexed (RVESVi) > 80 mL/m^2, and/or right ventricular end diastolic volume indexed (RVEDVi) > 160 mL/m^2, and/or progression of tricuspid regurgitation (TR) to at least moderate
  - Progressive RV systolic dysfunction.
  - RVOTO with RVSP >80 mmHg

PR, pulmonary regurgitation; PVR, pulmonary valve replacement; RV, right ventricle; RVEDVi, right ventricular end diastolic volume indexed, RVESVi: right ventricular end systolic volume indexed; RVOTO, right ventricular outflow tract obstruction; RVSP, right ventricular systolic pressure; TR, tricuspid regurgitation.

Allograft. Transplantation of human pulmonary valves (known as allografts or homografts) that are obtained from cadavers or from diseased hearts started over 50 years ago. These valves had very good outcomes in terms of hemodynamics, reduced thromboembolic risk (even without anticoagulants), low immunogenicity and a better resistance to endocarditis than mechanical or bioprosthetic valves.[18] However, the use of this kind of valves has some handicaps starting with the restricted availability, due to the lack of donors, as well as the limited durability, since only 30%-40% of homograft valves are still functional after 20 years of implantation. These limitations are even more evident in pediatric patients in which valve degradation is even faster. It is considered that the way homografts are preserved and some residual immunogenicity may promote valve degeneration leading to lower durability of this category of valves.[18,19]

For a long time homografts have been considered the first choice for PVR in ToF patients as they show excellent results in long-term durability in adults.[20] The event-free survival is not so good since an important part of patients tend to develop cardiac arrythmias. On the other way, homografts show frail results in children with ToF due their association to early re-operations.[21]

Pulmonary homografts can also be used in the Ross procedure for RVOT reconstruction. It is an accepted strategy to treat pediatric patients and young adults with aortic valvular disease and has excellent results as, the long-term survival is comparable to the general population. However, a pulmonary homograft dysfunction may require a re-operation.[22] According to American College of Cardiology and American Heart Association more than 50% of pulmonary homografts will require reinnervation in 10-20 years.[23] Despite that, in Oeser et al. freedom from pulmonary homograft reoperation was 87.5% in 20 years. Patient's age in the most relevant factor that interferes with pulmonary homograft durability as in patients older than 35 years, freedom from reoperation in 20 years was 97.1%, while in pediatric patients was 67.5%.[22]

Bioprosthetic. Bioprosthetic heart valves are easily available, have excellent hemodynamics (comparable to homografts) and, also, do not need anticoagulation.[24,25]

It is known beforehand that the longevity of this type of prosthesis is limited, and therefore multiple reinterventions may be required. Although there is limited information in the pulmonary position, in several studies the cumulative incidence of reinterventions was between 10% and 35%. According to Egbe et al. the 15-year cumulative incidence of prosthetic

valve dysfunction was around 48% in adults.[26] These valves are known to perform poorly in children, and younger ages are considered a risk factor for re-intervention.[25,26]

As far as ToF is concerned, bioprosthetic valves have worse outcomes than homografts, since the latter is associated with lower transvalvular gradient, lower incidence of structural valve deterioration and lower reinterventions.[20]

Mechanical Valve. Most patients, especially children, that require PVR do not receive a mechanical valve in the pulmonary position. Instead, pulmonary homografts, or bioprosthetic valves are preferred since they have good durability and do not need anticoagulation. However, mechanical valves can also be suitable in pulmonary position. It is considered that patients who benefit the most from these valves are the one who already need anticoagulation for another reason, patients who had already numerous cardiac surgeries or patients who have already undergone PVR in which the valve had poor durability.[27,28]

When patients are correctly anticoagulated with warfarin, the incidence of thrombosis is low, ranging from 0% to 0.6% per patient-year. Regarding durability, Pragt et al. revealed 97% freedom of reoperation at 5 years and 91% at 10 years. Unlike homografts and bioprosthetic valves, no association was found between patient age at PVR and need for reoperation.[29]

Expanded Polytetrafluoroethylene Valved Conduit. As seen above, the problem of valvular aggression by the immune response in younger patients is transversal to homografts and bioprosthetic valves (the most type of valves used in PVR). To overcome this, attempts have been made to use synthetic ePTFE valved conduits due to their low immunogenicity and good biocompatibility.[30] In Yamagishi study, in which ePTFE valves conduits were used in younger patients only, 1.7% of patients were classified as having severe stenosis and reoperations were performed in 6.0% of patients (follow-up duration around 5 years). When a large caliber ePTFE valve conduit is used (18-24 mm) freedom from reoperation was 93.8% at 10 years, while using smaller caliber (6-16 mm) the rate 68.6% at 10 years. When using a smaller caliber conduit, its replacement is inevitable due to growth and body weight gain.[31]

Bovine Jugular Vein Conduits. Bovine jugular vein conduits (BJVC) were introduced to be an alternative to pulmonary homografts and are currently available for patients younger than 18 years. Recent evidence

demonstrates that BJVC has an 84%-90% 10-year freedom rate from explantation. Indeed, it is better when compared with the rate reported for traditional homografts (68%-84%) and similar to decellularized homografts (86%-100%).[32,33] Blanz et al. demonstrated that BJVC had better performance than homografts in infants. In infants (<1year), around 90% of the BJVC became dysfunctional 10 years after implantation, whereas homografts became dysfunctional only 4 years after implantation.[34]

However, is it also known that BJVC has a higher late endocarditis incidence, when compared to other valves.[35]

Hereupon, despite results from different studies were not consistent, BJVC have at least similar durability (or even better) than cryopreserved homografts.[33]

Bearing in mind what has been said, there are limitations that are transversal to the valves typically used in PVR, such as lower durability in younger patients and the inability of these valves to adapt to growth. This requirement to have valves that are able to grow, to provide a long lasting performance and to self-repair may be addressed by tissue engineered heart valves (TEHVs).[36]

Potential of Tissue Engineered Pulmonary Valves

The objective of producing TEHVs is to have a living valve that, as human valves, can adapt and remodel to environmental changes. These valves are particularly useful for children and young patients with CHD and pulmonary valve dysfunction.[37] A TEHV that is able to somatically grow as the child grows could potentially reduce the need for reoperations. This has become increasingly relevant as the life expectancy increasing of children with these diseases leads them to eventually "exceed" the life expectancy of traditionally used valves.[6,38,39]

Tissue engineered approaches generate models of biodegradable materials, extracellular matrix and/or embedded cells that should be robust so that they are ready to work once placed in demanding hemodynamic conditions. Once placed, resident cells must maintain and remodulate the extracellular matrix (ECM), allowing the growth and self-repair. To achieve this, there are 3 approaches to valve manufacture: In vitro, In vivo, and In situ tissue engineering[36] that are summarized in Figure 1.

In Vitro. This approach is based on the original paradigm defined by Langer and Vecanti to obtain a tissue engineered tissue.[40] It requires

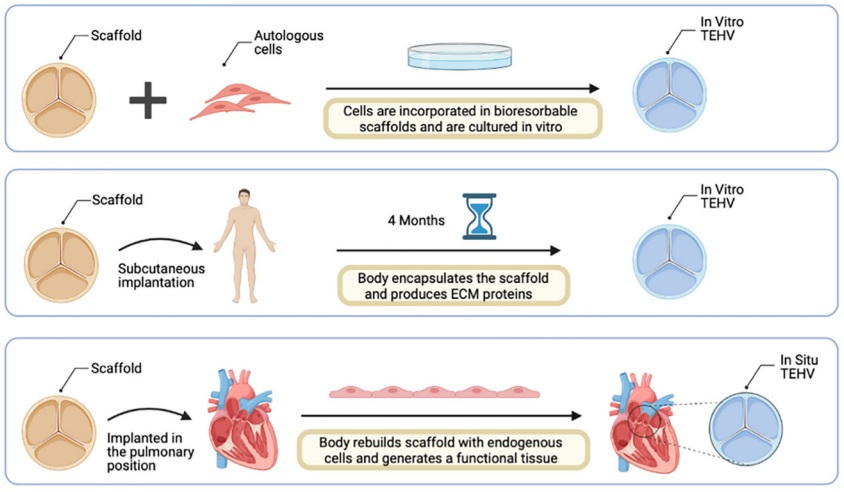

FIG 1. Tissue engineered heart valves (TEHVs) overview. In vitro—Autologous cells are incorporated in a bioresorbable scaffold and are cultured in vitro until a mature model is formed; In vivo—Scaffold is implanted subcutaneously for 4 months. When it is explanted, it can be used as a pulmonary valve autologous replacement; In situ—A scaffold is implanted in pulmonary position. Autologous cells will rebuild the scaffold and form a functional valve. ECM, extracellular matrix; TEHV, Tissue engineered heart valve.

autologous cells, scaffolds, and stimuli to create a cellularized valve in the laboratory, before implantation. Cells are incorporated in bioresorbable scaffolds and are cultured in vitro until a mature model that has sufficient elasticity and strength is formed. This maturation is often aided by mechanical or biochemical stimulation to promote tissue synthesis and organization. Then TEHV produced in vitro are implanted.[36,41]

However, long term results in animals have been suboptimal due to valve leaflet retraction, adverse in vivo remodeling, and valve failure. Furthermore, this method requires complex procedures that are logistically challenging, time consuming and expensive, so alternatives, such as in vivo and in situ approaches are essential.[6,39,42]

In Vivo. The in vivo approach takes advantage of the body's capacity to encapsulate external materials and to produce extracellular matrix proteins upon subcutaneous implantation of a nondegradable valve-shaped scaffold.[42,43] When the tissue-encapsulated scaffold is explanted, it can be used as an autologous replacement that is nonimmunogenic, non-toxic and may have growth and regenerative abilities.[44]

Despite the ingenious way in which this valve is developed it has some limitations, such as the inability to control the type of tissue surrounding the mold or the fact that the formation of the surrounding tissue requires at least 4 months of subcutaneous implantation.[41,44,45]

In Situ. In this approach a cell-free scaffold is implanted in the pulmonary position, relying on the body's capacity to rebuild the scaffold with endogenous cells to generate a functional tissue. When compared with the previous methods, this one is cheaper and less complex, representing an attractive economic proposition.[42]

The key factor in this method is the material used as a scaffold. Those materials can be biodegradable polymers (natural or synthetic) or ECM derived scaffolds (decellularized homografts, decellularized xenografts or in vitro-derived ECM-based TEHVs).[46]

Biodegradable polymers are simple and fast to produce while having substantially reduced costs as they do not require any donor tissue, in vitro cells, or tissue culture. These materials have some good advantages since they can be implanted via catheter techniques and can be designed to last enough time, keeping functional while endogenous tissue is forming. At this moment, synthetic polymers are those that are being studied more assertively due to their positive outcomes in clinical and preclinical trials, unlike natural polymers which had poor outcomes.[39,44,46]

ECM-derived scaffolds are based on ECM from native human valves (homografts), animal valves (xenografts) or from in vitro TEHVs. These scaffolds are obtained by removing the cell components by decellularization. They have advantages as biocompatibility and physiological-like mechanical properties and structure. Xenografts based scaffolds clinical trials had poor results as those valves caused severe inflammatory responses and valve calcification. In contrast, TEHV with homografts based scaffolds have had very promising outcomes, and that is why they are being studied more closely.[44,46,47]

As an alternative for homografts and xenografts, scaffolds based on in vitro TEHV were investigated. It has also some good results as it may help to overcome the leaflet retraction associated with in vitro grown TEHV.[44]

In Tables 3-5 there is an overview of results of clinical studies regarding the use of decellularized homografts, decellularized xenografts and biodegradable scaffolds in the pulmonary position.

TABLE 3. Decellularized homografts results overview

Study (y)	Type	Participants	Main results
Pulmonary homograft dysfunction after the Ross procedure using decellularized homografts[48] (2020)	Multicenter study	- 466 patients underwent a Ross procedure - Mean age 47 ± 12 y - Median follow-up is 2.2 y	- Cumulative incidence pulmonary homograft dysfunction (PHD) was 11 ± 2% at 6 years, mainly due to PS (93%) - Cumulative incidence of homograft reintervention was 3 ± 1% at 6 y - Patient age <45 years was the only independent risk factor associated with PHD ($P = 0.03$)
A European study on decellularized homografts for pulmonary valve replacement: initial results from the prospective ESPOIR Trial and ESPOIR Registry data[49] (2019)	Clinical trial	- 121 patients participate in the trial - Mean age 23 ± 14.4 y - Mean follow-up of 2.2 ± 0.6 y - Total combine DPH cohort (Trial + Registry data): 235 patients	- Primary efficacy end points mean peak gradient and regurgitation were excellent after a 2 y follow-up - There were 2 early deaths and no late mortality (1.7% mortality) - 1 reoperation was required for recurrent subvalvular stenosis - The combined DPH cohort, showed significantly better freedom from explantation (DPH 96.7 ± 2.1%, CH 84.4 ± 3.2%, $P = 0.029$ and BJVC 82.7 ± 3.2%, $P = 0.012$) and less structural valve degeneration (DPH 61.4 ± 6.6%, CH 39.9 ± 4.4%, $P = 0.87$ and BJVC 47.5 ± 4.5%, $P = 0.029$) at 10 y when matched to Cryopreserved homografts (CH) and Bovine jugular vein conduits (BJVC)

(*continued on next page*)

TABLE 3. (*continued*)

Study (y)	Type	Participants	Main results
Fresh decellularized versus standard cryopreserved pulmonary allografts for right ventricular outflow tract reconstruction during the Ross procedure: a propensity-matched study[50] (2018)	Clinical trial	- 130 patients with a DPH, median age 28 y - 130 patients with CH, median age 30 y - Up to 8 y follow-up	- DPH and CH used for RVOT reconstruction in the Ross procedure are associated with comparable 8 y freedom from allograft dysfunction (DPH 86.7% vs CH 87.3%, $P = 0.183$) and freedom from allograft reintervention (DPH = 99.2% vs CH = 97.6%, $P = 0.642$)
Decellularized fresh homografts for pulmonary valve replacement: a decade of clinical experience[51] (2016)	Clinical Trial	- 93 patients with a DPH - 93 patients with a CP - 93 patients with a BJVC - Mean age at DPH implantation was 15.8 ± 10.21 y	- At 10 y, the rate of freedom of explantation was 100% for DPH, 84.2% for CH ($P = 0.01$) and 84.3% for BJVC ($P = 0.01$). - Mid-term results of DPH for PVR confirm earlier results of reduced re-operation rates compared with CH and BJVC

BJVC, bovine jugular vein conduits; CH cryopreserved homografts; DPH, decellularized pulmonary homograft; PHD, pulmonary homograft dysfunction; RVOT, Right ventricular outflow tract.

TABLE 4. Decellularized xenografts results overview

Study (y)	Type	Participants	Main results
Long-term results after the Ross procedure with the decellularized AutoTissue Matrix P bioprosthesis used for pulmonary valve replacement[52] (2018)	Clinical study	- 492 patients underwent a Ross procedure - Mean age 56.7 ± 10.7 y - Mean follow-up 7.7 ± 4.3 y	- Survival rates at 5, 10, and 12.5 y were 82.8%, 70.4%, and 62.4% respectively - Freedom from pulmonary valve reoperation at 5, 10 and 12.5 y was 76.2%, 58.6%, and 53.4%, respectively - Long-term results showed a high rate of reoperation/reintervention for structural pulmonary valve failure
Early and late failure of tissue-engineered pulmonary valve conduits used for right ventricular outflow tract reconstruction in patients with congenital heart disease[53] (2012)	Clinical study	- 93 patients - Median age and weight at operation were 20 mo and 10.15 kg - Median follow-up duration of 12 mo	- 35.5% of patients experienced conduit failure whereas conduit dysfunction occurred in 29% - 2 y freedom from conduit failure and dysfunction was 60.2% (95% confidence Interval: 50.1-69.6) and 77.4% (95% confidence Interval: 67.9-84.7), respectively - Compared with the other conduit for RVOT reconstruction Matrix P conduits showed a high incidence of failure
Formation of multiple conduit aneurysms following Matrix P® conduit implantation in a boy with tetralogy of Fallot and pulmonary atresia[54] (2014)	Case report	- 6-y-old boy with ToF and pulmonary atresia - Conduit implanted at the age of 16 mo	- 5 y later he developed severe stenosis of the distal conduit anastomosis
Adverse results of a decellularized tissue-engineered pulmonary valve in humans assessed with magnetic resonance imaging[55] (2013)	Clinical Trial	- 26 patients - Median age of 12.4 y	- 52% required valve replacement due to graft failure after 19 mo of implantation - The high frequency of graft failure can be related to inflammation and fibrosis

RVOT, right ventricular outflow tract.

TABLE 5. Biodegradable scaffolds results overview

Study (y)	Type	Participants	Main results
Study to Assess Safety of the Pulmonary Valved Conduit (PV-001) in Subjects Undergoing Right Ventricular Outflow Tract Reconstruction (Ongoing)	Clinical trial	- Actual enrollment: 12 participants	- Estimated study completion date: April 2022
Xeltis Bioabsorbable Pulmonary Valved Conduit Pivotal Study - Xplore2 (ongoing)	Clinical trial	- Estimated enrollment: 56 participants	- Estimated primary completion date: December 2023 - Study completion date: December 2026
A Novel Restorative Pulmonary Valve Conduit: Early Outcomes of Two Clinical Trials[56] (2021)	Clinical trial	- All patients completed 12 mo of follow-up Group 1 - 12 pediatric patients - Median age 5 y (2-12) Group 2 - 6 more children were included	- At the beginning were 12 participants. During the study leaflet design was modified and 6 more children were added that received a new updated XPV (Xeltis pulmonary valve) - All children are in NYAH function class I - 17 children (of 18) show no evidence of progressive stenosis, dilation, or aneurysm formation - 5 patients in group 1 developed severe PR due to leaflet prolapse - Only 1 patient developed more than mild PR in group 2 and it was not due to leaflet prolapse
Initial Clinical Trial of a Novel Pulmonary Valved Conduit[57] (2021)	Clinical trial	- 12 participants - Median age 5 y (2-12)	At 24 mo: - None of the patients has required surgical re-intervention - 9 of the 12 are in NYHA functional class I and 3 patients in NYHA class II - None of the conduits has shown evidence of progressive stenosis, dilation, or aneurysm formation - 5 patients developed severe PR (the most common mechanism was prolapsed of at least one of the valve leaflets)

PR, pulmonary regurgitation; XPV, Xeltis pulmonary valve.

Discussion

Decellularized homografts are the TEHVs in which we have more information and promising results. However, their limited availability is the major limitation, being transversal to all homografts.

Although it has not yet been possible to create the ideal bioresorbable material, in situ TEHV are extremely promising. They are not dependent on donors or cell cultures, being easier to produce and much more economically attractive.[42,44] Beyond what has already been mentioned, patients with CHD may require multiple invasive surgical procedures during their lifetime and that why transcatheter valve replacement techniques have emerged. They are a less invasive, nonsurgical procedure to replace heart valves and can be applied to TEHVs.[37]

Hereupon, combining noninvasive techniques with a valve capable of growing, remodel and adapting to pediatric patients opens new possibilities to increase the quality of life and the longevity of pediatric patients and also, to become the basis for the future management of CHD that require PVR.[37,42,44]

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