Xenografts and Tissue Engineered Heart Valve in Pediatric Cardiac Surgery. Quo Vadis, Once More?

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Abstracts: *Introduction:* Many attempts have been undertaken for surgical correction of congenital heart defects. Reconstruction of the right ventricular outflow tract (RVOT) is a main component of many procedures. Homograft devices are considered as benchmark, but these are in short supply. Xenografts and tissue engineered heart valves (TEHV) have been proposed as solution. This review aims to explore what progress has been made for these two alternatives.

Methods: A systematic search for TEHV and the commonly used xenograft (Matrix P / P+, Shelhigh and Contegra) devices through ISI web of Knowledge was performed. The SynerGraft homograft was also included.

Results: Contegra, Shelhigh and Matrix P / Matrix P+ have been used with varying success. The problems are foreign body reaction, with inflammation, stenosis of the conduit or more distally in the pulmonary arteries and regurgitation. In spite of efforts during more than 20 years, TEHV has not left the laboratory: there is still an ongoing search for the ideal scaffold, adequate cell sources for cellular repopulation and culture media. There are no long-term animal models for the latter device.

Conclusions: To treat patients with congenital heart disease, reconstruction can be performed with xenograft devices, but their limitations have to be taken into account. Matrix P and P+ as well as Shelhigh suffer from inflammation with stenosis. The alternative, TEHV, will not be available for the foreseeable future. In any case, any TEHV device has to compete against more established values.

Keywords: Congenital heart valve defect, Homograft, Right ventricular outflow tract, Tissue engineering, Xenograft.

INTRODUCTION

The treatment of congenital heart disease can be performed by repair, reconstruction or replacement of valves and outflow tracts, especially at the right side. If a valve replacement is needed in such procedures, there are two main types of devices: mechanical and biological. The most often used contemporary mechanical devices are bi-leaflet valves. For biological devices, the homograft can be considered as gold standard, but these are in limited supply. In contrast, porcine xenograft, bovine pericardial and some other devices are off the shelf. These devices, however, have not the capacity to grow with the patient. A valve repair is another approach, but this requires the patients' own tissues of sufficient quality, which is not always at hand. For this reason, tissue engineered heart valves (TEHV) are under development. These constructs are designed to avoid deterioration (which is the main complication of a biological prosthesis) or thromboembolic events (which is the main complication of mechanical valves) [1]. Moreover, implantation of a living device should, make in-vivo repair after implantation possible. The TEHV under development are 1) decellularized biological matrices, with or without reseeding, 2) fibrin based scaffolds and 3) biodegradable synthetic scaffolds with reseeding [2].

Before 2005, there were no published results of bioresorbable matrices in patients. These devices are considered as being not biomimetic [3]. Also, negative results tended not to be published. Hybrid approaches with collagen, completed with glycosaminoglycans and elastin did produce publications, however. Before 2005, its standardization was still ongoing [2]. The use of a-cellular matrices were also unsuccessful, since these do not "revitalize" [4]. Moreover, the use of the CryoLife Synergraft, a decellularized xenograft at that time, resulted in disaster and was withdrawn [5]. A more recent review discussed the use of biodegradable scaffolds, cell seeding, maturing in bioreactors and implantation of a-cellular devices [6]. *In vivo* studies, however, remained few in number and all are of short-term duration. As alternative, some devices with xenogeneic origin have been developed. Sometimes, these are also called TEHV since these underwent some processing. One could wonder if decellularization process suffices to label this as TEHV. The research question for this review can be formulated as: "What are the results of four of the most commonly used commercially available devices in the repair and reconstruction of congenital heart defects" and "What has been the progress in development of TEHV in the period 2010-2014".

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METHODS

A systematic review of literature was performed using "ISI web of knowledge" database, for a 5-year time span between 2010 and 2014. For the first track, the search terms were "Tissue Engineered Heart Valve AND pediatr* OR paediatr*". The items of interest were the matrices, either synthetic of biologic, the cell sources for repopulation, the culturing conditions, and in case of animal studies, the hemodynamic *in vivo* and immune-histochemical data after explantation. For the second track, the search terms included "Contegra AND right ventricular", "Shelhigh AND right ventricular", "Synergraft AND right ventricular", "Matrix P and right ventricular" as decellularized devices most in use. The items of interest were the grafts themselves, the indication for operation, age at operation, hospital mortality, duration of follow-up, freedom of mortality, dysfunction and failure, mean transvalvular gradient across the pulmonary valve, pulmonary valve regurgitation over 2/4, re-intervention and reoperation rate. Reviews, state-to-the-art papers and papers not concerning the topic were excluded.

RESULTS

The search for the first track resulted in 29 manuscripts. There were fourteen reviews, three papers were about other issues, and remarkably, two papers, dealing with the Matrix P device [7,8] overlapped with track 2. Of the remaining ten papers, seven were "*in vitro*" experiments and three were "in-vivo" animal studies. The "in-vitro" papers dealt with several topics: decellularization of a porcine root [9], assembling tri-layered scaffolds by electrospinning [10], self-assembling of a tri-leaflet valve [11], use of fibrin with a valve-like mechanical conditioning structure [12], the rate of degradation of different types of synthetic scaffolds with respect to deposition of new matrix proteins and the mechanical properties [13], culturing of valve interstitial cells on synthetic scaffolds [14], and the use of prenatally harvested cells from umbilical blood and of amniotic fluid or chorionic villi [15]. The parameters under investigation were a) microscopy to detect inflammation or fibrosis, b) immunoh-istochemistry to identify the different cell types, c) biochemistry to identify the different types of collagen, of glycosaminoglycans and of DNA, d) gene expression, e) transmission electron microscopy as well as f) anisotropic biomechanical properties. The "in-vivo" papers dealt with spontaneous in-vivo regeneration of decellularized in pigs [16], comparison of cell sources (endothelial, smooth muscle and bone marrow) with respect to inflammation, calcification and hemodynamic parameters after percutaneous implantation in sheep [17], and comparison of the effect of two types of culture mediums on recellularization and the potential contractile activity of the reseeded cells [18]. The parameters under investigation were hemodynamics *in vivo* and immunohistochemistry or transmission electron microscopy after explantation.

The search for the second track resulted in 33 manuscripts concerning decellularized devices. These were explored for their demographic, clinical and hemodynamic results (Table). Most papers were description of the results of one device. The SynerGraft has been included as an example of homograft. Earlier implantations of xenogeneic SynerGraft devices [5] had disastrous results. Decellullarized SynerGraft homograft seems less immunogenic and therefore more durable than the standard homograft for RVOT reconstruction in patients with mean age of 18 years. It is considered as superior for the Ross procedure in aortic valve replacement in terms of dysfunction, failure (defined as peak transvalvular gradient of over 40 mmHg or pulmonary valve regurgitation of more than grade 2) and explantation [19-21]. However, longer follow-up duration is needed to establish its durability. Some consider the advantages as "not significant" and hence the additional costs not justified [22]. The decellularized pulmonary homograft seeded with autologous endothelial cells in a small series of younger adults showed good clinical and hemodynamic results, with absence of calcification at 10 years [23]. This device could be considered as real tissue engineering because of the cell seeding. Decellularized fresh pulmonary homograft had better results in terms of reoperations and hemodynamics compared to glutaraldehyde fixed bovine jugular vein (BJV) or cryopreserved homograft. An adaptive growth has been observed in the former [24].

The Matrix P / P+ conduit is a glutararaldehyde-free decellularized porcine conduit with valve and cell free pericardial patch mounted on a stent. These devices could be considered as TEHV, with a presumed capacity for growth. Matrix P and Matrix P+ devices for reconstruction of the RVOT failed early in the very young, mostly due to inflammation with subsequent stenosis: freedom of failure at two years was about 60%. Autologous cell seeding in the explanted specimens was poor [7] and endothelial cell-ling was absent [8]. The inflammation was described as massive and of foreign-body type with infiltration by B and T cells, as well as macrophages and extensive fibrosis

Table 1: Valve Type, Demographic Data, in-Hospital Results and Long-Term Results

REF	Device	n	Indication	Age	H-mort (%)	FU(y)	y	Mort	Dysf	Fail	mTVG	PI>2	Reint	Reop
[7]	Matrix P / P+	93	RVOT	20	4.3	1	2	-	-	22.6	39.8	-	4	27%
[19]	standard	61	RVOT	18.6		5.7	-	13%*	48%	32%	-	32%		22%
	decell SG	39	"	"		5.8	-	10%*	26%	13%	-	10%	-	8%
20]	standard	29	Ross AVR	28.6	0	4.9	-	0	0	-	12	0	-	37(8)
	decell SG	34	"	"	0	"	-	0	0	-	12	0	-	21(8)
[21]	conventional	665	Ross	28.3	3.9	3.7	5	5.2	-	3.7	-	-	4.5	5.6%
	conventional	581	RVOT	5.2	8.4	3.7	5	15.4	-	10.7	-	-	10.5	8.6%
	decell SG	193	Ross	32.4	1.6	4.0	5	3.1	-	6.1	-	-	5.6	3.0%
	decell SG	581	RVOT	13.4	2.7	4.0	5	7.7	-	6.6	-	-	7.3	2.4%
[22]	standard	47		9.9			8	2%	-	22 (10)	-	37%	13/47	12/47
	decell SG	47		9.9			8	4%	-	16 (25)	-	21%	9/47	9/47
[26]	Matrix	61	RVOT	7	8.2		3	-	13	-	-	-	9/62	4/62
[27]	Matrix P+	16	RVOT	14	0	0.8	1	-	-	-	66	-	-	38%
[28]	Contegra	244	RVOT	4.7	0.8		1	5.3%	-	-	-	-	-	3.7%
							5	7.2%	-	-	-	-	-	20.7%
							7	10.0%	-	-	-	-	-	35.8%
							10	10.0%	-	-	-	-	-	62.9%
	homografts	135	"	1.7	2.2	3.7	1	9.6%	-	-	-	-	-	5.4%
							5	10.5%	-	-	-	-	-	24.3%
							7	10.5%	-	-	-	-	-	31.4%
							10	13.2%	-	-	-	-	-	41.7%
[29]	Contegra	106	Ross &RVOT	13	3/106	7.6	7	4.3%	-	-	-	-	-	-
[30]	Homograft	62	RVOT	<1			5	-	14.6%	-	-	8.3%	-	30.6%
							10	-	40.8%	-	-	35.2%	-	-
	Contegra	35	"	<1			5	-	24.9%	-	-	26.4%	-	40.6%
							10	-	64.2%	-	-	55.8%	-	-
	Hancock-porc	48	"	<1			5	-	30.9%	-	-	13.1%	-	46.2%
							10	-	50.3%	-	-	47.9%	-	-
[31]	Contegra	18	RVOT	9	16.7%	2	-	-	2/15	-	50	2/15	2/15	-
[32]	ven homogr	20	RVOT				)	comparable concerning catheter intervention, reoperation or either						
	valve homogr	16	"			)		comparable concerning catheter intervention, reoperation or either						
[33]	Four types	56	RVOT		14.2%	1.8	-	1/44	-	15/44	26-67	-	3/44	-
[34]	Contegra	16	CHD		3/16		-	-	-	1/12	-	-	1/12	2/12
[35]	TA repair	19	RVOT	0,2	21.1%	1.8	-	-	6/15	-	-	0	4/15	-
[36]	Contegra	34	RVOT	10.9	0	7.1	11.4	-	-	-	19.6	8-27	-	6%
[37]	Contegra	156			7%	4.8	8	10.1%	15.1%	-	18.7	25/145	-	13/145
[38]	Contegra	193	RVOT-Ross	6.7	NA	4.6		2.6%	-	-	-	-	5.2%	2.6%

							10	-	-	10%	-	-	-	-
[39]	All	286	RVOT	5.9	2.7%									
	homograft	88					-	-	-	-	14-13**	3	-	benchmark
	Monocusps	67					-	-	-	-	16-18	5	-	-13%
	Bicuspid	44					-	-	-	-	46	2	-	+78%
	Contegra	40					-	-	-	-	18-36	3	-	+59%
[40]	Homogr comp	66		6.4	0	9.4	9	-	-	-	12.6	3.4%	-	14.3%
	Homogr incomp	54		"	0	9.4	9	-	-	-	"	"	-	37.0%
	Contegra	85		4.8	2*	5.3	9	-	-	-	14.2	7.2%	-	11.0%
[41]	All devices	167	RVOT		17%	6.5	(3.5)	-	-	-	-	-	-	22.1%
[42]	Shelhigh	57	RVOT	18	4	3.1	2	-	-	-	76	-	-	18%
	Contegra	43	RVOT	4.5	8	5.7	2	-	-	-	69	-	-	9%
[43]	Contegra	54	RVOT	10.4		6.0	1	-	-	-	-	-	-	1.9%
							5	-	-	-	-	-	-	22.7%
							10	-	-	-	-	-	-	36.5%
	Homograft	293	RVOT	13.4		5.9	1	-	-	-	-	-	-	0.4%
							5	-	-	-	-	-	-	6.0%
							10	-	-	-	-	-	-	18.6%

AVR: aortic valve replacement; comp: blood group compatible homograft; decell: decellularized; dysf : dysfunction ; fail : failure; FU: mean follow-up time for the group; hosp mort: hospital mortality; incomp: blood group incompatible homograft; mTVG : mean transvalvular gradient; n: number; PI : pulmonary valve insufficiency; reinterv: re-intervention; reop: reoperation; RVOT: right ventricular outflow tract; SG: SynerGraft; ven homogr: venous homograft; TA: truncus arteriosus; y: years referring to freedom of mortality, of dysfunction, of failure, or re-intervention or reoperation.
* death not graft related; ** first value children >1 y; second: infants; definition of dysfunction; mean TVG > 30 mmHg; definition of failure: mean TVG > 40.

[8, 25]. Others, however reported results comparable to other commonly used devices, with a 3-year freedom of re-intervention rate of 87% [26]. However, early failures of this so-called tissue engineered pulmonary device, implanted in mostly teenagers warrants caution [27]. Incomplete decellularization could contribute to an increased immunogenicity [25].

The Contegra device is a glutaraldehyde fixed bovine jugular (BJV) construct containing a valve. The Contegra for repair of the RVOT (right ventricular outflow tract) is more prone to bacterial endocarditis, conduit deterioration and reoperation at mid-term in infants compared to the homograft devices. Predictors for re-replacement were endocarditis and age of less than 3 years at first implantation [28, 29]. Durability for the Contegra device seems comparable to that of homografts and porcine valved Dacron constructs in infants, but implantation during the neonatal period or in heterotopic position decreases its durability. Moderate stenosis and regurgitation occurs sooner [30]. Tetralogy of Fallot as indication, systemic-to-pulmonary shunt and hypothermia were identified as predictors for these events. The treatment of endocarditis, which occurs in 11.3-12.5% of the patients is surgical [29]. Use of the Contegra device in cases with pulmonary atresia, ventricular septal defect combined with hypoplastic pulmonary arteries [31] as well as for the Fontan procedure should also be considered with caution. Valved femoral homograft devices could be considered as attractive alternative in neonates who need reconstruction of the RVOT [32]. Some authors report an acceptable outcome, with occurrence of mild-to-moderate stenosis in 40-50% of the cases. This can often be treated by catheter based intervention. Anyway, long-term results need to be awaited [33-36]. Contegra device for RVOT reconstruction has acceptable results, but reoperation is more common due to small size, which can be related to young age and expected patient growth. However, there is a freedom from calcification and an only moderate increase in mean transvalvular gradient from 10 to 19 mm Hg [37, 38]. The Contegra device can be considered as valid alternative for pulmonary homograft devices [38]. A homograft, however has

50% lower rate of reoperation [39], unless this homograft is non blood group compatible. A Contegra could be a valuable alternative if a compatible homograft cannot be found [4], however need for intervention because of failure caused by conduit stenosis must be anticipated [38].

Some papers compared the results between several devices. In one manuscript, the Shelhigh was compared with Contegra, Cryolife, Aortech and some less often used devices. These implants were used for a variety of indications. The hospital mortality (17%) and need for reoperation (22%) were high. The Cryolife and Shelhigh implants had the shortest re-operation time. The Contegra performed better [41]. In another comparison between Shelhigh and Contegra, this was confirmed: Shelhigh failed more rapidly and strongly. The most prominent indication for implantation was the tetralogy of Fallot. For both devices inflammation with subsequent stenosis was the predominant mechanism. Mean time for reoperation was 1.5y for the Shelhigh group and 3.5y for the Contegra group for patients with a mean age of 12y. No predictors for failure could be identified. However, endocarditis was more common with Contegra: 7% versus 1.8% for Shelhigh [42]. The higher incidence of endocarditis was also confirmed in a comparison between homograft devices and the Contegra device. Furthermore, the predictors for re-replacement were small size, young age, heterotopic position and use of Contegra – twice as much compared to homograft [43].

DISCUSSION

There are several options for the surgical treatment of congenital heart defects. These are homograft, xenograft and TEHV devices. Although considered as superior, homograft devices are in short supply, especially for the smaller sizes, needed for the repair of such defects. The results seem even better if these homograft devices are decellularized [19] and if these are blood group compatible [40]. An excellent animal (ovine) model, in which the RVOT was reconstructed, showed the superiority of pulmonary homograft over an aortic homograft and certainly over porcine xenografts: after six months the devices were explanted. The pulmonary homograft showed little or no calcification. There was some calcification in the aortic homograft and much more in the porcine devices [44]. The lack of homograft devices, especially those of small size, leaves the two options, namely TEHV and xenografts. The difference between both options must clearly be established. In two papers [7, 8], the Matrix P / P+ is called a tissue engineered heart valve. However, one could wonder if decellularizing a tissue, with the hope of repopulation by host cells after implantation is enough to call this tissue engineering. A possible definition given in 2002 states the following “The application of principles and methods of engineering and life sciences to obtain a fundamental understanding of structure-function relationships in novel and pathological mammalian tissues and the development of biological substitutes to restore, maintain or improve tissue function” [45]. It seems, that in practice, the Matrix device falls short of this definition.

The first option, TEHV shows some peculiarities: at least half of the papers recently published about TEHV in pediatric cardiac cardiology are reviews. Most of the research papers deal with “in-vitro” studies [9-15], which seem all promising. But it has become clear that, after more than 20 years of research, it remains a promise: the ideal matrix (biological or synthetic origin) still has to be developed and the ideal cell source or sources still have to be identified. Work on the most appropriate culture mediums and biomechanical conditions is also unfinished. One could wonder if the “silver bullet” is ever to be found. Only three papers deal with short-term animal studies [16-18]. A fourth, comparative study also lasted only 6 months [44]. Some results seem promising concerning repopulation by cells of the host, absence of fibrosis, inflammation thrombosis and stenosis or regurgitation. The main limitation, however, is the short duration of the experiments, which is three to 15 months. Furthermore, not much has been written on the changes of the implanted devices within the living animal. Last but not least, companies are not inclined to introduce uncertain devices which, on the one hand, have to compete with established values with a predictable outcome, and on the other hand, could lead to disaster.

Every device within the second option has its own problems. Two papers of the first track [7, 8] and another of the second track [27] deal with the Matrix P and P+ device. The results warrant caution in its use. The Contegra shows acceptable results, but endocarditis has been repeatedly identified as a problem [28, 29, 42]. The Shelhigh device is susceptible to a quicker and stronger inflammatory response which leads to fibrosis and stenosis [41, 42].

CONCLUSIONS

Congenital heart disease is a difficult problem to treat. For the moment, the use of homograft devices seem to be the best option. Because these are in short supply, xenografts have been used as an alternative. Most of these xenografts have their specific problems: inflammation and rapid failure for the Shelhigh and Matrix P / P+ and endocarditis for the Contegra. These devices show no somatic growth. A second alternative, the use of tissue engineered devices is for this moment purely theoretical. Although efforts to develop a viable product which theoretically can grow with the patient, are ongoing for 20 to 30 years, it is still in the laboratory stage. Animal experiments are few, all with a short follow-up. Methods to evaluate the in-vivo changes of such devices in living animals are still lacking. Even if an tissue engineered device would be available today, it would still have to prove its time-consuming claims against the existing devices.

LIMITATIONS

There are several limitations in this manuscript. First, there is a wide variety in congenital heart defects. Little attention has been paid to this aspect. Nevertheless, one major observation can be made: heterotopic implantation of a device leads to worse results. Second, only the most commonly used xenografts have been included. Although this may be arbitrary, their results can be considered as representative. Third, the manuscripts included have different designs. Some are retrospective, others are prospective. Still others are experimental, in-vivo as well as in-vitro. This precludes any quantitative analysis. Fourth, there was no quality control of the manuscripts included. This might have one advantage: their results represents, the “real life”, also outside the Western world.

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CONFLICTS OF INTERESTS

None to declare

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