Performance of SynerGraft Decellularized Pulmonary Allografts Compared with Standard Cryopreserved Allografts: Results from Multi-Institutional Data

(Short title: SynerGraft versus Standard Allografts)

Steve Bibevski, MD, PhD[1]

Mark Ruzmetov, MD, PhD[2]

Randall S. Fortuna, MD[2]

Mark W. Turrentine, MD[3]

John W. Brown, MD[3]

Richard G. Ohye, MD[1]

From the University of Michigan School of Medicine, Ann Arbor[1], Michigan,
Children Hospital of Illinois, OSF Saint Francis Medical Center, Peoria, Illinois[2],
Indiana University School of Medicine, Indianapolis, Indiana[3]

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Address reprint request to:

Richard Ohye M.D
C.S. Mott Children's Hospital
Rm 11-742
1540 E. Hospital Drive SPC 4204
Ann Arbor, MI 48109-4204
Telephone: 734-936.4978 or 877-262-4628
e-mail: ohye@umich.edu

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Background. Structural deterioration of allografts over time is believed to be related at least in part, to an immune response mounted against human leukocyte antigen specific to the transplanted tissue. SynerGraft processing is a technology that decellularizes an allograft leaving only connective tissue therefore reducing immunogenicity and potentially increasing durability of the implant.

Methods. We performed a retrospective review of one hundred sixty-three SynerGraft patients and one hundred twenty four standard allograft controls from three medical centers. Patient demographics were tabulated and conduit stenosis and insufficiency were measured by echocardiography.

Results. There were twenty-eight deaths (SG, 15/163 9% vs standard, 13/124 11%; P= 0.72) but no death was attributed to structural failure of the conduit. The actuarial survival for Synergraft versus standard cohorts was not different at 5 and 10 yrs. Among the 274 hospital survivors, 17% SG versus 42% standard had evidence for significant conduit dysfunction at the most recent follow-up or before conduit replacement. Freedom from conduit dysfunction was significantly worse at 10 years in the standard group (58%) as compared with SG (83%, P<001).

Conclusions. This study represents a multi-institutional retrospective comparison of Synergraft and standard cryopreserved allografts used in RVOT reconstruction in a broad range of patient ages. Our results demonstrate that at an intermediate to long term follow-up, conduit dysfunction and pulmonary insufficiency and stenosis are higher among patients receiving standard allografts. We postulate that the improved durability of SG is related to decreased immunogenicity of the SG technology.

INTRODUCTION

Cryopreserved pulmonary allografts play an important role in both adult and congenital heart operations involving reconstruction of the right ventricular outflow tract (RVOT). Early results with standard cryopreserved allografts (SCAs) for reconstruction of the RVOT in congenital heart disease have been good, but there are long-term studies reporting allograft dysfunction and failure. Structural deterioration of allografts over time is believed to be related at least in part, to an immune response mounted against human leukocyte antigen (HLA) specific to the transplanted tissue. Indeed, host antigen recognition and antibody development is increasingly linked to development of tissue calcification and structural valve deterioration, and humoral antibodies are known to develop against HLA that are specific to the transplanted conduit.

SynerGraft processing (SG; CryoLife, Kennesaw, GA) is a proprietary technology that decellularizes an allograft leaving only connective tissue which may then repopulate with host cells therefore reducing immunogenicity. Clinical reports have demonstrated a significant reduction in the immunologic response in recipients of SynerGrafts as measured by panel-reactive antibody levels compared to recipients of standard cryopreserved allografts(1, 2). Furthermore, previous data comparing standard allograft to SynerGraft has demonstrated an improved profile in terms of conduit failure; however these have been from single institutions and included limited numbers of patients (1, 3-5). In addition, data from single institutions can be influenced by particular techniques in use, as well as different eras within institutions encompassing changing surgeons and other practices. The purpose of this project was therefore to assess the durability of the SynerGraft-processed allografts compared with standard cryopreserved allografts using data from multiple institutions.

MATERIALS AND METHODS

Study patients

The medical records of all patients undergoing RVOT reconstruction with the insertion of an SG or standard cryopreserved pulmonary allograft conduit from 2000 to 2010 at C.S. Mott Children's Hospital at University of Michigan, Ann Arbor, Michigan USA (n=82), James Whitcomb Riley Children's Hospital at Indiana University, Indianapolis, Indiana, USA (n=111) and Children's Hospital of Illinois, OSF Saint Francis Medical Center at University of Illinois, Peoria, Illinois, USA (n=94) were retrospectively reviewed. The Institutional Review Board (IRB) at each institution approved this study and all IRBs waived the need for patient consent.

One hundred sixty-three SynerGraft patients and one hundred twenty four standard allograft controls were evaluated. The choice of conduit was made preoperatively or in the operating room by the surgeon without randomization. The choice of type was not based on any particular protocol, but largely on availability. All allografts were obtained from CryoLife (Marietta, GA, USA). Blood group matching could not be accommodated because allograft availability in sizes appropriate for this patient population was extremely low. Conduit size was determined according to the calculated Z value for each implanted valve using the valve diameter compared with the normal value with the general goal of inserting a conduit with a Z score of +1 to +3. This was achieved in 80% of patients with no patients receiving a negative Z score conduit.

Demographic information, cardiac anatomy, preoperative hemodynamics, operative details and postoperative outcomes were recorded retrospectively from patient records. All surviving patients were examined by their referring cardiologist in the immediate postoperative period and reexamined with serial transthoracic echocardiography approximately every 6 months or 1 year until December 2012. Transthoracic echocardiography was used to evaluate conduit gradients and the degree of pulmonary insufficiency. The cardiologist performing echo assessment was not aware of the type of conduit implanted.

Conduit stenosis was assessed by the measurement of peak velocity through the valve using continuous wave Doppler technique. Pulsed color-flow Doppler was used to detect pulmonary insufficiency (PI) by the evaluation of a regurgitant jet. The peak and mean systolic gradient were measured using the modified Bernoulli equation. PI was classified mild if there was retrograde diastolic flow in the conduit and less than 1 cm regurgitant jet in the RVOT; moderate if retrograde diastolic flow was detected in the conduit with a 1-2 cm regurgitant jet in the RVOT; and severe if additional retrograde diastolic flow was detected in the branch pulmonary arteries with a greater than 2 cm jet in the RVOT. Valve regurgitation was quantified as none/trivial, mild, moderate and severe using grades 1, 2, 3 and 4, retrospectively. Freedom from pulmonary insufficiency was defined as grade 2 or less. Freedom from pulmonary stenosis was defined as the peak echocardiographic Doppler RVOT gradient less than 40 mm Hg by two-dimensional echocardiography at any level within the RVOT. Freedom from conduit reintervention was defined as no need for surgical repair, replacement and/or intervention with balloon dilatation or stent placement. Conduit dysfunction was considered to be present if the peak echo Doppler gradient was greater than 40 mmHg by two-dimensional echocardiography at any level within the RVOT and/or grade 3 or 4 conduit valve insufficiency.

Surgical Technique

All patients underwent median sternotomy, with standard cardiopulmonary bypass techniques. Intracardiac repair was performed during aortic cross-clamping with intermittent cold blood cardioplegia, while conduit insertion was performed with the cross-clamp removed and the heart beating during rewarming. The outflow end of the allograft conduit was cut as short as possible to position the conduit valve at the distal anastomosis well to the left of the sternum. The proximal anastomosis was augmented anteriorly using a hood of autologous pericardium or GoreTex.

Stenosis in a branch pulmonary artery was relieved employing a patch of bovine or autologous pericardium or GoreTex. Postoperatively, patients receiving allografts were given ibuprofen postoperatively at Peoria

and Indianapolis. All patients were treated with a minimum of 6 months of aspirin (10 mg/kg/day) at discharge.

Statistical analysis

Data are presented as the mean $\pm$ SD. Continuous variables were analyzed with Student's t-test and categorical variables using the chi-square test. Variables for the two cohorts were compared using two-tailed unpaired t-test and Kaplan-Meier curves for actuarial survival, freedom from conduit insufficiency, and freedom from conduit reintervention. End points were time of death, first diagnosis of conduit insufficiency or stenosis, interventional or surgical re-intervention and conduit replacement, respectively. The log-rank test was used to estimate the statistical difference between the two types of conduits. The significance level was set at a P value of $\leq$ 0.05. Early death was defined as death in the hospital or within 30 days of discharge. All other deaths were considered late.

RESULTS

The patient demographics are summarized in Table 1. There were no significant differences in sex, number of orthotopic or heterotopic insertion, concomitant procedures, previous surgery on pulmonary valve or preoperative diagnoses including Ross / non-Ross coefficient). Weight and valve diameter were significantly higher in patients with SynerGrafts when compared with standard allografts ($p= 0.01$ and <0.001, respectively). Patients receiving standard allografts were significantly older than those receiving Synergraft ($p=0.01$). The frequency of RVOT allografts insertion during the study interval is shown in Figure 1.

The time on the extracorporeal circuit and the global ischemic times were similar. The mean conduit size was from 19-22 mm for both groups (Table 1), but a significantly greater number of patients received standard allografts in sizes 8 to 12 mm (Figure 2).

Follow-up

All surviving patients were examined by their referring cardiologist in the immediate postoperative period and reexamined with serial transthoracic echocardiography approximately every 6 months or 1 year until December 2012. Follow-up was 94% in both cohorts. For SGs, the mean follow-up was 60.1 ± 37.1 months, ranging from 1 month to 10 years, with a median follow-up of 5 years. The mean follow-up for standard allografts was not significantly different at 60.3 ± 35.9 months, ranging from 0 months to 10 years, with a median of 5.5 years ($P=0.97$). Early death was defined as death in the hospital or within 30 days of discharge. All other deaths were considered late.

Mortality

There were twenty-eight deaths (SG, 15/163 9% vs standard, 13/124 11%; $P= 0.72$). 13 early deaths (SG, n=8 and standard, n=5) and 15 late deaths (SG, n=7 and standard, n=8). No death was attributed to structural failure of the conduit. The actuarial survival including hospital deaths for SG and standard cohorts at 5 years

(SG, 94%; standard, 94%) and 10 years (SG, 91%; standard, 89%) was similar for both groups (P=0.84) (Figure 3).

Freedom from conduit dysfunction

Among the 274 hospital survivors, 76 subjects (SG, 26/155, 17%; standard, 50/119, 42%) had evidence for significant conduit dysfunction at the most recent follow-up or before conduit replacement. Freedom from conduit dysfunction was significantly worse at 10 years in the standard group (58%) as compared with SG (83%, P<001).

Freedom from conduit re-intervention

At latest follow-up, 16 subjects (10%) in the SG group exhibited conduit failure (surgical re-intervention, n=9; percutaneous re-intervention [PCI], n=6; and one subject had both PCI and surgery) secondary to stenosis and/or valve dysfunction. The mean time to re-operation in the SG group was 43.1±26.8 months (range: 1-96 months). Percutaneous re-interventions were required in seven patients (balloon dilatation, n=5 and stent implantation, n=2); of these, one subject required surgical conduit re-implantation at 2 years post PCI intervention.

Conduit failure was observed in 32 of 119 (27%) standard allografts subjects (surgical re-intervention, n=28; percutaneous re-intervention, n=4; and one patient had both PCI and surgery). The mean time to re-operate for standard group was 37.0±32.0 months (range: 0.5-120 months) and was not significantly different from the SG group (P=0.51). At 10 years post-implantation, the freedom from conduit re-intervention was higher in the SG group, and the difference was significant (P=0.001; Figure 4).

Conduit retention and function at last follow-up

The peak gradient across the conduit and the degree of pulmonary insufficiency are shown in Table 2. Echocardiographic data at follow-up showed an overall low pressure gradient across the pulmonary valve,

but significant differences between the two groups, with the SG conduits demonstrating a lower peak pressure gradient compared with standard allografts (SG, 20.7±15.7 mmHg vs standard 27.4±18.7 mmHg; P=0.003). Mean echocardiographic degree of conduit regurgitation of the SGs (1.8±0.9; ranges 0 to 4) was significantly less than that of standard allografts (2.3±1.1; ranges 0-4; P<0.001) (Figure 5).

Sub- group analysis

We examined the performance of size 12 mm and less (SG, n=14; standard, n=24). Survival was similar (SG, 71%; standard, 67%; P=0.76). Freedom from conduit dysfunction was 36% (4/11) in the SG group, but only 5% (1/21) in the standard group (P= 0.02). Freedom from conduit re-intervention was significantly higher in SG group compared with standard group (50% vs 12%, P=0.03), respectively. The incidence of allograft reintervention in subjects with a size of 17 mm and less (SG, n=36; standard, n=42) was also significant higher in standard allograft sub-group (SG, 9/36 (25%); standard, 23/42 (55%); p=0.01). Similarly, the incidence of allograft reintervention in subjects with larger sizes (> 18mm) was higher in the standard sub-group, but did not reach statistical significance (SG, 7/19 (6%); standard, 9/77 (11%); p=0.19).

We also compared the performance of conduits inserted primarily in subjects less than 1 year of age (SG, n=27; standard, n=39). Survival was 82% in SG group and 74% in standard group (P=0.50). Freedom from re-intervention (SG 63%; vs standard 39%; P=0.07) was better in the SG cohort, but did not reach statistical significance. Freedom from conduit dysfunction (SG 54%; vs standard 19%; P=0.005) and freedom from significant insufficiency were significantly higher in the SG group (SG 63% vs standard 22%, P=0.002, respectively).

COMMENT

The use of allografts for reconstructing right ventricle to pulmonary artery continuity is common in the modern treatment of patients with congenital heart disease despite limited availability and the option of xenograft conduits. Driving this use has been the relatively good longevity of allografts and expected excellent hemodynamic and valve performance. Numerous studies have now been published documenting the expected life of implanted conduits, with clearly documented early failure secondary to conduit obstruction and valve leaflet destruction (6, 7). Indeed, accelerated degeneration has been observed for pulmonary allografts in younger children, the very population that relies on these conduits the most (8, 9). This study represents a multi-institutional retrospective comparison of SGs and standard cryopreserved allografts used in RVOT reconstruction in a broad range of patient ages. The primary objective was to compare durability and conduit function using the two technologies over time as evaluated by echocardiography. Our results demonstrate that at an intermediate to long-term follow-up, conduit dysfunction and conduit insufficiency and stenosis are higher among subjects receiving standard allografts, with no difference in actuarial survival. In addition, our data shows that there is a greater freedom from conduit dysfunction in smaller sized conduits and younger subjects with the SG conduits. Sub-analysis further shows that the time to failure is the same between groups suggesting that the benefit of SG technology is found in fewer conduits that progress to failure or intervention rather than a delayed time-course. We postulate that the improved durability of SG is related to decreased immunogenicity of the SG technology.

Allograft conduit failure is now largely attributed to an immune mediated process which in large part is likely related to donor specific antigens on the conduit. Rajani and colleagues (10) have identified cellular rejection in allograft material removed from children undergoing replacement of previously placed allografts. Similar results were reported by Vogt which demonstrated T-cell mediated rejection removed from the pediatric population, but interestingly, the presence of cellular rejection was much lower in allografts

removed from adults (11). Prospective measurement of HLA class I PRA in children undergoing surgery with or without the implantation of allograft material has demonstrated that the PRA increased within three months of surgery while the control group had no significant change in PRA (12). To reduce antigenicity, Synergraft technology utilizes a technology which decellularizes the tissue leaving behind a collagen matrix which significantly reduces the immunologic response but leaves behind a functional vascular matrix available for autogenous remodeling. Migration of recipient specific cells into the matrix should ultimately render the material indistinguishable from other endogenous tissue and there is evidence of such a process in sheep implanted with porcine valves. Obrien and Elkins (13) reported that after 4-6 months, histologic assessment showed progressive recellularization of the conduit and valve leaflets with host fibroblastoid cells and subsequently with mature interstitial cells without evidence of calcification in animal models. Whether this actually happens in humans is unlikely based on the appearance of excised allografts, however the histologic assessment of explanted conduits from humans has not been well documented.

Elkins has however reported that the humoral immune response to decellularized allografts in human subjects is improved with SG (14). Of 57 subjects that had negative PRA at the time of implantation of SG, 77 % continued to have negative PRA. Of the 11 pediatric subjects that were PRA negative, all remained negative post SG implant. Da Costa demonstrated that decellularized allografts are less antigenic than standard allografts wherein they could not detect any elevation in antibody and PRA levels in 7 cases and only marginal elevation in 2 subjects (15).

There is growing evidence that the decreased immune reactivity described above translates into better allograft longevity. In a short term study of mean 19 months follow up, Tavakkol demonstrated that SG had greater durability with less insufficiency and lower gradients in their cohort of 26 patients (16). The same group later presented a cohort of 41 patients at intermediate follow up at 46 months and showed greater freedom from moderate –to-severe insufficiency in the SG group, and in patients older than 2 years of age, the SG valves demonstrated less regurgitation and stenosis (17). Despite these promising reports on the

benefits of decellularizing the allograft, there have been a number of reports which have shown no difference between SG and standard allograft. Bechtel et al have published a number of papers which compared SG to conventional allografts and have found no statistically significant difference in conduit longevity with only slight trends towards improved peak gradients in smaller conduits (18, 19). Interestingly, our data shows a clear benefit in the smaller sizes, and statistical significance weakened with the larger sizes. This suggests that the studies showing no difference between the SG and standard cohorts may have been underpowered to detect an effect since all of their patients were adults with larger allografts. This point serves to highlight the importance of conduit size selection. In our study, over 80% of patients in both groups were implanted with a z score of +1 or greater, and a goal of +2 should be selected if possible.

The retrospective nature of this study resulted in limitations with respect to data collection, because information on several variables may not available for all patient subjects. The SG subjects were heavier, had larger grafts and were younger in age, however any biases should have been addressed in the subgroup analyses. Because this study includes data from three institutions, it may also contain limitations and bias in data related to echocardiographic findings in each institution where different cardiologists reviewed the echos. Strict criteria for assignment of values of PI and stenosis were utilized, as described in the methods, and were based on echocardiographic standard procedures. We did not perform a specific analysis looking at differences based on preoperative diagnosis, however benefits for longevity have been suggested by a number of earlier studies, and avoidance of increased antibodies is a worthwhile return regardless of preoperative diagnosis. Finally, our study design did not allow for us to determine differences between practices, however each institution has published independent data previously.

In summary, the data from this multicenter study demonstrate a benefit in the longevity of pulmonary allograft conduits treated with the SG decellularization process compared to standard allografts. These findings are largely consistent others with the reported literature. This study also found that these benefits were magnified in the pediatric population.

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FIGURE LEGENDS:

Figure 1. Distribution of implanted SGs and standard allografts operation during study period.

Figure 2. Distribution of implanted SGs and standard allografts diameters

Figure 3. Kaplan – Meier estimated 10-year survival, including hospital mortality.

Figure 4. Kaplan – Meier estimated 10-year freedom from conduit reintervention.

Figure 5. Kaplan – Meier estimated 10-year freedom from pulmonary insufficiency.

Table 1. Demographics

	SynerGraft (n=163)	Standard Allograft (n=124)	P value
Age (months, mean)	20.7.6±197.8	151.5±171.5	0.01
(range)	(2d - 74 years)	(3d – 56 years)	
Weight (kg; mean)	45.8±36.3	35.2±32.7	0.01
(range)	(2 - 126 kg)	(1.9 – 160 kg)	
Gender (M/F)	107/56	69/55	0.09
Orthotopic / Heterotopic	69(42%)/94(58%)	52(42%)/72(58%)	0.94
Preoperative diagnosis			
AVD / Ross procedure	68 (42%)	44 (36%)	
Tetralogy of Fallot	26 (16%)	29 (23%)	
PA/VSD	15 (9%)	14 (11%)	
Truncus arteriosus	25 (15%)	8 (7%)	
TGA	15 (9%)	15 (12%)	
Other	14 (9%)	14 (11%)	
Previous surgery on PV	68 (42%)	49 (40%)	0.71
Initial/repeat allograft insertion	125/38	96/28	1.00
Ross/non-Ross patients	68/95	44/80	0.28
Concomitant procedures	138 (85%)	104 (84%)	0.86
Valve Diameter (mm; mean)	22.1±5.8	19.5±6.0	<0.001
Z-score of implanted valves	1.3±1.9	1.1±1.1	0.45
Cardio-pulmonary bypass time (min)	147±87	152±75	0.65
Cross-clamp time (min)	90±59	89±71	0.94

Legend: AVD – aortic valve disease; M – male; F- female; PA – pulmonary atresia; PV – pulmonary valve; TGA – transposition of the great arteries; VSD – ventricular septal defect

Table 2. Degree of pulmonary stenosis and pulmonary insufficiency at last follow-up

	SynerGraft	Standard Allograft	P value
Pulmonary stenosis (mm Hg; mean)	20.7±15.7	27.4±18.7	0.003
Pulmonary insufficiency (degree; mean)	1.8±0.9	2.3±1.1	<0.001