

Pulmonary Arterioplasty With Decellularized Allogeneic Patches

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Background. Decellularized allogeneic nonvalved pulmonary artery patches for arterioplasty are a relatively new option compared with cryopreserved allogeneic, crosslinked xenogeneic bioprosthetic or synthetic materials. This study examines the midterm experience with a new decellularized allogeneic patch for congenital cardiac reconstructions.

Methods. For this prospective postmarket approval, nonrandomized, inclusive observational study, we collected data on a consecutive cohort of 108 patients with cardiovascular reconstructions using 120 decellularized allogeneic pulmonary artery patches (MatrACELL; LifeNet Health, Inc, Virginia Beach, VA) between September 2009 and December 2012. One hundred of the patches were used for pulmonary arterioplasties. Two patients were lost early to follow-up and excluded from subsequent survival and durability analyses. Data included demographics, surgical outcomes, subsequent reoperations, and catheter reinterventions. These variables were also collected for an immediately preceding retrospective consecutive cohort

of 100 patients with 101 pulmonary arterioplasty patches who received classical cryopreserved pulmonary artery allografts (n = 59 patches and patients) or synthetic materials (n = 41 patients with 42 patches) for pulmonary arterioplasties between 2006 and 2009.

Results. In 106 patients with 118 decellularized patches, there were no device-related serious adverse events, no device failures, and no evidence of calcifications on chest roentgenograms. In contrast, the prior comparative pulmonary arterioplasty cohort of 100 patients experienced an overall 14.0% patch failure rate requiring device-related reoperations ($p < 0.0001$) at mean duration of 194 ± 104 days (range, 25 to 477 days).

Conclusions. The intermediate-term data obtained in this study suggest favorable performance by decellularized pulmonary artery patches, with no material failures or reoperations provoked by device failure.

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Pulmonary arterioplasty is a frequent component of complex congenital cardiac reconstructions. Multiple materials have been used, including synthetics (eg, polytetrafluoroethylene [PTFE]), manufactured bioprosthetics (eg, glutaraldehyde or photo-crosslinked xenogeneic tissues), cryopreserved allogeneic vascular tissues, and autologous tissues (eg, pericardium), with the latter fresh or briefly crosslinked with glutaraldehyde in the operating room [1]. None of these possess all of the requisite desirable properties: unlimited resource, thickness and compliance matching similar to native tissues, scaffold properties that promote autologous recellularization with subsequent matrix remodeling, noninflammatory, nonreactive, nonthrombogenic, and immunologically benign, with optimal surgical handling characteristics and good sutureability [2, 3]. Such characteristics are sought to optimize the initial repair and to reduce the frequency of repetitive pulmonary arterial reconstructions or catheter-based dilations or stenting, or

both, that are frequently required to preserve patency of these hypoplastic vessels that often fail to grow and resist interventions, with scarring and stenosis at repair sites [4, 5].

Thus, many different strategies, including various patch materials, have been tried for use in reconstructing and maintaining vessel caliber with the intent of encouraging rather than retarding growth of the pulmonary artery tree [6]. This report describes the midterm outcomes of a prospective clinical study of a 5-year experience by a single pediatric cardiovascular service with the use of decellularized allogeneic pulmonary artery patches for cardiovascular reconstructions, with particular emphasis on pulmonary arterioplasty procedures in neonates and infants [7].

Patients and Methods

Institutional Review Board approval was obtained for this study. Waivers were obtained from the Institutional Review Board for parental permission, patient assent, and Health Insurance Portability and Accountability Act authorization. In September 2009, after United States Food and Drug Administration 510k clearance,

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MatrACELL decellularized pulmonary artery patch allografts (LifeNet Health, Virginia Beach, VA) became commercially available for surgical repairs of the right ventricular outflow tract for patients of all ages.

The decellularization process uses an anionic, non-denaturing detergent (sodium lauroyl sarcosinate) to solubilize and remove the donor cells and a recombinant endonuclease (Benzonase, EMD Millipore, Billerica, MA) to degrade donor DNA/RNA [8]. These are followed by a recirculating water washout using an ion exchange resin bed to facilitate removal of detergent and cellular remnants. The final step uses glycerol to replace the water volume in the tissue to facilitate vitrification and frozen storage at -80°C or colder.

This decellularized pulmonary artery allogeneic human allograft acellular extracellular matrix is supplied in three formats: thin patches, thick patches, and hemipulmonary arteries (includes contiguous vessel wall from main and branch pulmonary arteries). This study examines the inclusive first 3 years of experience of a single pediatric cardiovascular institution with the use of this novel human tissue-derived patch material for cardiac reconstructions in neonates, infants, and children.

To insure that the total surgical series (108 patients with 120 patches) was inclusive and consecutive, data were collected on all patients in our institution who received MatrACELL patch repairs beginning with the first patient on September 9, 2009, enrolling and analyzing all consecutive patients undergoing the index operations up to December 31, 2012. By study design, patients will continue to be enrolled until September 2014. The following variables were collected on these individuals: all device-related and nondevice-related serious adverse events (SAEs), including death, stenosis, or patch aneurysmal dilation; postoperative complications; basic demographic data, including congenital diagnosis, sex, and age at time of the operation; and patch detail, including number, thickness, and location of all patches. Operative mortality was defined as death within 30 days after the operation (The Society of Thoracic Surgeons definition) [9].

The durability analysis excluded 2 patients with two pulmonary arterioplasty patches who have been lost to follow-up and for which only perioperative data are available. For the remaining 106 patients (118 patches), all anticipated (staged) operations, all patch revisions or replacements, unanticipated reoperations, and all catheter-based reinterventions were captured. The last three event types were considered SAEs and then adjudicated to determine if device-related or not.

All postoperative imaging studies and operative and cardiac catheterization data were reviewed for evidence of structural abnormalities developing at the sites of patch reconstructions or elsewhere in the target vessels. All SAEs identified by anatomy that could potentially be associated with the surgical patch repairs were independently re-reviewed and adjudicated by 3 cardiac surgeons, including review of postoperative angiograms, echocardiograms, computed tomography or magnetic resonance imaging, reoperative surgical and catheterization reports, and chest roentgenograms.

To further focus the comparison on just pulmonary arterioplasty, the patch durability or freedom from reoperation for patch failure in the decellularized pulmonary arterioplasty subgroup with full follow-up ($n = 91$ patients receiving 98 patches) was compared with 100 patients in whom pulmonary arterioplasty had been performed with 101 patches fashioned from synthetics, primarily PTFE, or from cryopreserved pulmonary artery allografts. These comparison data were compiled from a retrospective cohort of all similar surgical pulmonary arterioplasty procedures from January 1, 2006, through September 8, 2009 (ie, consecutive patients before initiating the use of MatrACELL).

For the Western blot analysis of representative MatrACELL and cryopreserved valve conduit tissues, 30 μg protein was separated by 4% to 15% precast linear gradient polyacrylamide gel. To directly visualize the molecular weights, MagicMark XP Western Protein standard (Invitrogen, Inc, Carlsbad, CA) was similarly separated. Electrophoresis was followed by electroblotting onto a nitrocellulose filter membrane overnight at 4°C . After blotting, protein-binding sites were blocked in 5% nonfat dried milk. The filter was washed twice in phosphate-buffered saline and treated with a 1:25000 dilution of rabbit monoclonal anti-major histocompatibility complex-1 primary antibody (ab52922; Abcam, Cambridge, MA) in 5% nonfat milk for 1 hour at room temperature. After three washes, the filter was incubated with a 1:25000 dilution of the secondary antibody (goat anti-rabbit immunoglobulin G horseradish peroxidase; ab97069) in 5% nonfat milk for 1 hour at room temperature. Proteins were detected using enhanced chemiluminescence Western blotting detection reagents (GE Healthcare, Pittsburgh, PA).

Data are expressed as mean \pm standard deviation and median (range). Categorical data were compared with the two-tailed Fisher exact test. Survival curves were generated to describe patient freedom from surgical revision for patch failure and compared by Mantel-Cox, Breslow-Day, and Tarone-Ware proportional hazards tests for equality of survival distributions using PASW 18 software (SPSS/IBM Corp, Armonk, NY).

Results

Patient Outcomes With Decellularized Patches: Prospective Series

The mean age at the time of operation for the total prospective series of 108 patients receiving 120 decellularized patches was 367 ± 655 days (range, 7 to 4,758 days), and mean weight was 7.4 ± 6.17 kg (range, 2.38 to 50.00 kg). Total hospital length of stay averaged 61 ± 44 days (median, 12 days; range, 1 to 3,312 days) and was 29.7 ± 43.9 days (median, 12 days; range, 3 to 308 days) for survivors to hospital discharge. Sternal closure was delayed in 36 patients, and 5 required perioperative extracorporeal membrane oxygenation support. A total of 120 patches were placed with a variety of primary cardiac diagnoses (Table 1). Patches were used most often in various

Table 1. Diagnoses of Patients Receiving Decellularized Allogeneic Patch Repairs

Cardiac Diagnoses	Patients (No.)
Tetralogy of Fallot	23
Transposition of the great arteries	15
Hypoplastic left heart syndrome	12
Coarctation of the aorta	11
Pulmonary atresia	
Intact ventricular septum	8
Ventricular septal defect	5
Double-outlet right ventricle	5
Truncus arteriosus/interrupted aortic arch	4
Atrioventricular canal defect	5
Heterotaxy syndrome	3
Total or partial anomalous pulmonary venous return	3
Tricuspid atresia	3
Atrial septal defect/ventricular septal defect	2
Pulmonary artery stenosis	2
Anomalous origin of coronary artery from pulmonary artery	1
Aortopulmonary window	1
Ebstein anomaly	1
Interrupted aortic arch	1
Pulmonary stenosis, valvar	1
Single ventricle	
Double-inlet left ventricle	1
Total anomalous pulmonary venous connection	1

pulmonary artery locations (100 patches in 93 patients because 7 patients had 2 patches; Table 2). Seventeen patches were used in the neonatal aortic arch or for coarctation repairs, or both. Three rare uses included an intraatrial baffle, augmentation of an anterior mitral valve leaflet, and reconstruction of the roof of the left atrium.

For the 106 patients (118 patches) with complete follow-up, the median duration of implants was 687 patient-days (range, 1 to 842 patient-days), with a mean of 657 ± 442 patient-days. Operative mortality was 1.8%, of which no deaths were related to the patch reconstructions. Overall, 26 SAEs occurred in 20 patients, including 7 reoperations

Table 2. Types and Locations of Patches

Patch Type	Pulmonary Artery				Aortic Arch	Other
	Right	Left	Main	Bifurcation		
Hemi, ^a No.	1	3	15	3	8	1
Thick, ^b No.	1	3	26	3	8	0
Thin, ^c No.	11	1	26	7	1	2

^a Hemi patches are contiguous patches fashioned from main and left pulmonary arteries to retain the natural curvature. ^b Thick patches are fashioned from donor main pulmonary artery. ^c Thin patches are fashioned from donor branch pulmonary artery.

near the initial patch arterioplasty sites, 11 subsequent catheter angioplasties (3 in the aortic arch and 8 in the pulmonary arterial tree), and 8 patient deaths. None was attributable to the patch material, and none of the subsequent procedures addressing hypoplastic or stenotic vessels involved replacements or revisions of the patches per se. No patch fibrosis was identified in any patient.

For the 98 pulmonary arterioplasties in patients with follow-up, the most frequent sites of progressive pulmonary arterial narrowing were in the juxtaductal region but not involving an implanted patch (n = 8), progression of native pulmonary hypoplasia but not at the surgical patch site (n = 3), and stenosis at suture lines (n = 5), notably at shunt anastomoses (n = 4). No device-related SAEs occurred, and specifically, no pulmonary artery aneurysms or stenoses developed that were attributable to the decellularized patches or required replacement of the patches. There was no focal vessel narrowing or loss of caliber due to peel formation, scar fibrosis, or patch contraction.

The most recent imaging studies for all patients (chest roentgenograms, echocardiograms, etc) were reviewed specifically for evidence of mineralization, no calcification of the decellularized patches was revealed and none was specified in the final reports. Calcification of the patches was never observed at subsequent surgical staged repairs. Although some “thin” patches were observed to still be “thin” at elective reoperation, neither aneurysmal dilatation nor excessive inflammatory scarring of the patches has yet been observed.

Pulmonary Arterioplasty: Decellularized vs Retrospective Series of Cryopreserved Allogeneic and PTFE Patches

For an intrainstitutional post hoc comparison, all patients undergoing right ventricular outflow tract or pulmonary artery procedures, or both, were mined from the Heart Center Database for the 3.7 calendar years immediately before this study was initiated. During this period, 100 patients underwent pulmonary arterioplasty with 101 patches (42 synthetics and 59 cryopreserved homograft pulmonary artery tissue) and were anatomically and surgically similar to this present cohort. Failure of patch repairs requiring reoperation was documented in 14 patients (9 restenoses, 2 pseudoaneurysms, and 3 aneurysms and restenosis). No deaths were attributable to patch failures.

This preceding series, with an incidence of 14.0% reoperations for patch device-related failure when cryopreserved allografts or synthetics were used, is in marked contrast to the 0% found in the prospective decellularized series (p < 0.0001) at a median implant duration of 687 days. Reoperations for all but two of the retrospective patch failures were in patients who originally received cryopreserved allogeneic patch material. Two were patients with PTFE-related pseudoaneurysms. Comparing survival curves for the prospective 91 patients with 98 decellularized patch pulmonary arterioplasties with the retrospective 100 patients (101 patches) reveals that to date, there is 100% freedom from reoperation for

failure for the decellularized patches. The device failures in the retrospective group tended to occur within 16 months of the index operation; thereafter, the risk disappeared (Fig 1). Refining the analysis further and comparing failure rates only in patients undergoing pulmonary arterioplasties with the decellularized (0%) vs cryopreserved allogeneic tissue patches (20.3%) suggested much better results with the former ($p < 0.0001$). A range of findings involving the cryopreserved patches was noted at reoperation, including scar formation, fibrosis, calcification, and aggressive inflammation. These reoperations for “device failure” with the cryopreserved patches occurred at an average 194 ± 104 days (range, 25 to 477 days) postoperatively.

Comment

No decellularized patch related surgical failures were discovered in the first 28 months of use in pediatric cardiac reconstructions. However, not surprisingly in these diagnostic entities, 13 pulmonary arteries with subsequent hypoplastic growth and progressive diffuse or focal stenoses required additional surgical or catheter-based interventions after the initial patch placements [10]. None of these represented repairs or replacements of the initially placed patches but were in other anatomic locations, such as juxtaductal, related to shunt insertion sites, or were due to progressive regional longitudinal pulmonary hypoplasia with pulmonary arterial growth lagging somatic growth [5, 11–14]. Six patients required additional patches at a subsequent reoperation in different regions of the reconstructed hypoplastic pulmonary arteries. The fundamental pathophysiologies are

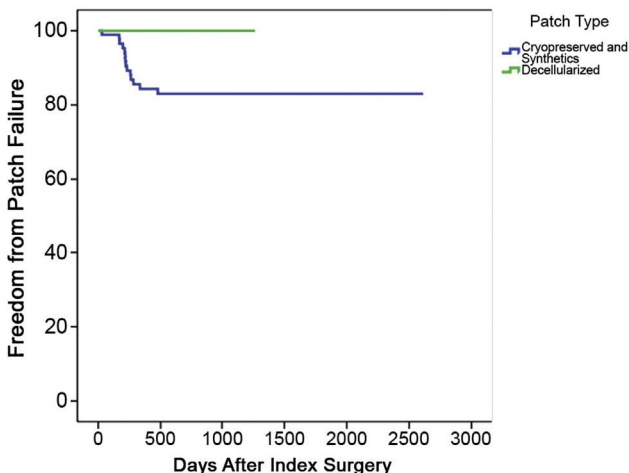


Fig 1. Pulmonary artery patch arterioplasty cumulative survival curves show freedom from reoperation for device failure for surviving patients in the prospective group that received decellularized (green) vs the retrospective group repaired with traditional synthetic patches (eg, polytetrafluoroethylene) or allogeneic cryopreserved pulmonary artery tissue (blue). Survival distributions are significantly different ($p < 0.001$) by proportional hazards regression analyses.

likely flow-related or molecular-based defects in programmed arterial growth. A subset of these is attributable to ductal tissue migration. Restrictive scarring from suture lines can further limit growth and exacerbate the proclivity for limited lumen enlargement over time. This is a known natural history, which is the reason pulmonary arterioplasty is typically extended beyond focal narrowing.

Although there were subsequent operations using additional new patch repairs in the prospective cohort, these did not involve replacement of “failed” original patches. All surgical and catheter reinterventions that anatomically could potentially have involved the patch repairs were re-reviewed by 2 independent cardiac surgeons as well as by the original operating surgeon to adjudicate precise anatomy, location relative to the original patch repair, explore potential technical issues, and to establish a putative etiology. These post hoc analyses did not identify any decellularized patch failures in the current series.

Other than the most commonly used cryopreserved allogeneic vascular tissues, alternative synthetic/bio-prosthetic materials for pulmonary artery reconstructions (eg, PTFE, glutaraldehyde crosslinked xenogenic tissues) tend to be thick and stiff. The retrospective failure rate for the synthetics (mostly PTFE) was 4.9%. These thicker and stiffer alternatives may be more applicable in older patients or to resist local compression that might threaten lumen diameter. The better compliance matching with the decellularized patches should result in less suture line torque, stress, and resultant fibrosis and contraction.

That decellularized arterial wall patches can potentially autologously recellularize suggests some possibility of collagen adaptive remodeling and, theoretically, even growth [7]. Calcification of xenogeneic pericardium and cryopreserved allogeneic tissues (both contain donor cell remnants) is a well-recognized natural history and is usually attributed to immune inflammatory processes especially as incited by transplant antigens [15, 16]. This should be minimized by the process of decellularization which, depending on the efficacy of the specific protocol, can remove the vast majority of the major histocompatibility complex antigens [17, 18]. To assess potential culprit residual transplant antigenic epitopes, Western blotting for human major histocompatibility complex was performed using protein extracts from clinical grade MatrACELL patch material and compared with cryopreserved pulmonary arterial tissue. The samples of decellularized tissue contained no demonstrable residuals (Fig 2). These results and the reported outcomes data together suggest that one likely mechanism for the improved performance is a reduction in antigenicity and related proinflammatory properties of the allogeneic sourced materials by decellularization [19–21].

In patients requiring pulmonary arterioplasty, there are five potential mechanisms for recurring or progressive pulmonary arterial stenoses and hypoplasia:

1. inherent provocation of inflammatory scarring/fibrosis by unfavorable patch materials,

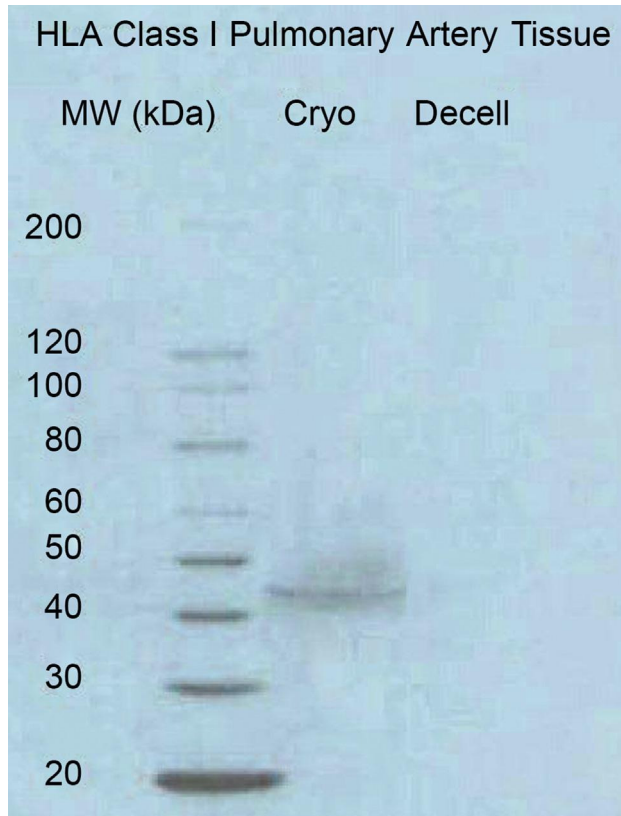


Fig 2. Cryopreserved pulmonary arterial tissues (cryo) contain retained cells; thus, the cryo lane (middle) demonstrates human leukocyte antigen class I major histocompatibility complex (MHC-I) antigen protein in the appropriate molecular weight (MW) window (left lane). Analysis of protein extracts from clinical grade decellularized pulmonary artery patches demonstrates no detectable MHC-I (right lane).

2. juxtarepair vascular tissue injury by sutures or application of vascular clamps provoking inflammation,
3. molecular mechanisms leading to defective growth and remodeling of the pulmonary arteries,
4. low blood flows, and
5. compliance mismatch between native and replacement vascular tissues [22, 23].

Only the first and last of these would be improved by the use of acellular allogeneic patch materials at the initial operation.

The strengths of this study include juxtaposed consecutive retrospective and prospective series in an inclusive 6-year interval with similar indications, diagnoses, surgical techniques, implanting surgeons, and follow-up in both cohorts [24].

The study has a few limitations. In the context of traditional cardiac replacement valve durability, 2 to 3 years would be considered short-term, but it was notable that most of the pulmonary artery patch failures in the retrospective group occurred within 1 year (Fig 1). Thus, patch angioplastic enlargement of the pulmonary arteries in neonates and young infants are most vulnerable

during this early steep allometric growth curve. If the repaired pulmonary artery growth is adequate by approximately 16 months after the operation, then patch failure appears to be unlikely. Thus in this context, these data are conceptually “midterm.”

The decellularized pulmonary artery patches are labeled as indicated for the pulmonary circulation, which was the most frequent application in this series. However, the shunted systemic circulation (as in hypoplastic left heart syndrome) in neonates has limits to the achievable peak systolic pressures due to the shunt runoff, which results in hemodynamic stresses similar to the pulmonary circulation. Thus, with this physiology, such neonatal aortic arch reconstructions are likely an appropriate and safe application. We have not used this material derived from human pulmonary arteries for systemic arterial reconstructions in 2-ventricle older infants, children, or young adults.

The early outcomes for pulmonary artery reconstructions can determine a patient’s future cardiovascular natural history [25]. The results in the first 18 months after the initial repair are especially important in neonates and infants because this is the time of the highest rate of somatic and cardiovascular allometric growth. It is the period during which troublesome development of pulmonary vessel stenoses and progressive hypoplasia is the most aggressive, and ultimately, determinative of blood flow distribution, ventricular workloads, and subsequent surgical strategies. No device-related failures in 98 decellularized pulmonary patches arterioplasties compares favorably with the 14.0% incidence of reoperations for patch “device failures” documented in the immediately prior consecutive 100 patients with 101 pulmonary artery reconstructions using other materials. In this reference group, the patch-related stenoses became apparent typically at approximately 9 months after the primary operation, a noteworthy observation given that these “midterm” results for the decellularized patches are at an average postoperative duration of 22 months. The mechanisms for these improved outcomes may include the reduction by decellularization of proinflammatory and immune provocative residuals as well as by better matching of viscoelastic properties to native vessels.

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INVITED COMMENTARY

Hopkins and colleagues [1] report the use of decellularized pulmonary homograft patch material in 106 patients, predominantly for pulmonary arterioplasty. No material related failure or reoperation was noted at 1.8-year follow-up. A historical group of 100 patients, having mostly cryopreserved or polytetrafluoroethylene (PTFE) patches for pulmonary arterioplasty, served as controls. The overall reintervention incidence was similar (17% study group versus 14% control group). Material failure was noted as the cause of reintervention in the control group. The authors also demonstrated that there were no residual antigens for major histocompatibility complex in the decellularized patch.

Among a number of things, ideal congenital vascular patch material would be nonantigenic and non-thrombotic, have good handling characteristics, have multidimensional distensibility, heal well and only along the suture line, and have durable tensile strength sufficient for use on either the left or right sides.

Current patch materials have some but not all of the ideal characteristics. Cryopreserved pulmonary homografts are antigenic and calcify. Porcine extracellular matrix can thicken with healing and is not uniformly reliable on the left side (personal experience). PTFE is not pliable and incorporates poorly. Autologous pericardium does not have multidimensional distensibility. Heterogenous pericardium develops porcelain calcification.

Decellularized pulmonary homograft material holds promise for each of the ideal patch characteristics, but not certainty. Of particular clinical interest is the subset of 17 patches used for aortic repair. A long-standing problem with hypoplastic left heart syndrome has been that a number of patients require transplantation after initial palliation. Palliative arch reconstruction has typically been performed with cryopreserved pulmonary homograft. The associated antigenic presentation results in elevated panel-reactive antibodies, which serve to complicate transplantation. A nonantigenic and multidimensionally