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Authors

Weng, Patricia L
Alejos, Juan Carlos
Halnon, Nancy
et al.

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Long Term Outcomes of Simultaneous Heart and Kidney Transplantation in Pediatric Recipients

Patricia L. Weng[1], **Juan Carlos Alejos**[2], **Nancy Halnon**[2], **Qiuheng Zhang**[3], **Elaine F. Reed**[3], and **Eileen Tsai-Chambers**[4]

[1]Division of Pediatric Nephrology, Mattel Children's Hospital UCLA, Los Angeles, CA, USA

[2]Division of Pediatric Cardiology, Mattel Children's Hospital UCLA, Los Angeles, CA, USA

[3]UCLA Immunogenetics Center, Department of Pathology and Laboratory Medicine, University of California, Los Angeles, CA, USA

[4]Division of Pediatric Nephrology, Duke University Medical Center, Durham, NC, USA

Abstract

Pediatric simultaneous heart and kidney transplantation (sHKTx) has become an effective therapy for patients with combined cardiac and renal failure. Often, these patients develop Human Leukocyte Antigen (HLA) antibodies from their previous allografts and are therefore more difficult to re-transplant. We describe the largest case series of a predominantly sensitized pediatric sHKTx with emphasis on medical management and patient outcomes. Demographics, clinical characteristics, antibody, and biopsy data were retrospectively collected from University of California, Los Angeles database and correlated with short and long-term patient and allograft outcomes of all sHKTx performed between 2002 and 2015. We identified 7 pediatric patients who underwent sHKTx at our center. Mean age at time of sHKTx was 13.7 years and 85.7% were re-graft patients. 57.1% were sensitized with cPRA > 50% and another 57.1% had pre-formed DSA. 5 year renal allograft survival and patient survival was 85.7% for both endpoints. The remaining 6 patients are all alive (mean follow up 78.5 months) with good kidney and heart function. sHKTx in a population with increased immunological risk can be associated with good long-term outcomes and offers potential guidance to the pediatric transplant community where data is limited.

Introduction

Pediatric simultaneous heart and kidney transplantation (sHKTx) has become an effective treatment for patients with combined cardiac and renal failure. The first adult simultaneous heart and kidney transplant was described in 1978[1] and the first pediatric sHKTx was performed in 1985 [2]. In the past few decades, the landscape of end stage renal disease

Corresponding author: Patricia L. Weng, 10833 Le Conte Ave, MDCC A2-383, Los Angeles, CA 90095, pweng@mednet.ucla.edu, telephone (310) 206-6987, fax (310) 825-0442.

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(ESRD) has shifted dramatically transitioning from primary renal disease to secondary organ dysfunction or systemic illness necessitating the need for a kidney transplant [3].

The complex pathophysiologic interactions between the heart and the kidney are multifactorial and may lead to primary dysfunction of either organ. More commonly, patients with low cardiac output myocardial dysfunction develop renal failure secondary to nephrotoxic immunosuppressive medications, infections and long-term ischemic renal hypoperfusion[4,5]. Often, these patients develop HLA antibodies from their previous allografts and are therefore more difficult to re-transplant[6-10]. Currently, there is limited information in the literature regarding indications, preoperative patient characteristics and outcomes of pediatric sHKTx. With the marked increase of sHKTx in the adult and pediatric population, including sensitized individuals[11], there is a growing need to understand the optimal treatment for these patients. Therefore, we report the largest case series of a largely sensitized pediatric sHKTx cohort with emphasis on medical management and patient outcomes.

Methods

Patient Selection and Evaluation

A total of 38 pediatric sHKTx have been performed in the United States since 1988 based upon OPTN data as of April 30, 2017.[12] Seven (18.4%) of these patients were transplanted at Mattel Children's Hospital at the University of California, Los Angeles (UCLA). This is a single center retrospective review of these 7 patients who were identified at our institution as recipients of sHKTx between 2002 and 2014. This retrospective chart review was performed in accordance with the UCLA institutional review board (IRB #16-000079) and is in accordance with the ethical standards outlined in the Helsinki Declaration of 1975. Demographics, clinical characteristics and follow-up data were collected from institutional databases and individual charts.

All 7 patients had concomitant, chronic end-stage cardiac disease and renal failure. Donors were matched for ABO blood type compatibility. Our criteria for sHKTx included eligibility for heart transplant to treat progressive symptomatic heart failure failing medical therapy with unacceptable risk for cardiac death within six months and sustained glomerular filtration rate (GFR) <50 mL/min/1.73 m^2 for more than 6 months. GFR was measured using radionuclide labeled diethylene-triamine-penta-acetic acid (DTPA) clearance corrected for body surface area prior to listing for sHKTx.

Clinical Protocols

Orthotopic heart transplantation was performed first per standard procedure. After stable hemodynamic status was established, kidney transplantation was performed within 24 hours following heart transplantation. With the exception of patient 1, who underwent sHKTx in 2002 when induction therapy was not routinely administered, the remaining six patients received either IL-2 receptor blockade or anti-thymocyte globulin (ATG) to delay initiation of a calcineurin inhibitor. Patients were maintained on steroid-based immunosuppression with tacrolimus and mycophenolate mofetil (MMF). Steroids were weaned to a maintenance

dose of 0.5 mg/kg with oral prednisone after hospital discharge. Tacrolimus goal trough levels immediately postoperatively were 10-12ng/ml, 8-10 ng/ml the first outpatient month, 7-8 ng/ml months 1-3 and 6-8 ng/ml after 3 months. MMF was started preoperatively at 600 mg/m^2/dose intravenously every 12 hours and then weaned to 450 mg/m^2 orally every 12 hours once tacrolimus levels became therapeutic.

Prior to sHKTx, desensitization was initiated in patients with calculated panel reactive antibody (cPRA) >50% or preformed donor specific antibody (DSA). The regimen was comprised of high dose intravenous immunoglobulin (IVIG) 2g/kg (maximum 144 grams) monthly for up to 4 doses. One dose of Rituximab 375 mg/m^2 and plasmapheresis for 5 days were added for patients with cPRA>80% or persistent DSA not declining with IVIG[13]. Complement dependent lymphocytotoxicity and flow crossmatches between the recipient and donor were performed at the time of transplant as previously described[14]. The threshold to proceed with transplantation post-desensitization therapy was a T cell flow crossmatch < 225 mean channel shift (MCS) and B cell < 250 MCS. Repeat HLA-mismatched class I and II antigens were intentionally avoided.

Post-transplant Monitoring

Protocol kidney transplant biopsies were done at 6 months, 1 year and 2 years post-transplantation. Protocol endomyocardial transplant biopsies were performed at scheduled times (1 week, 3 weeks, 3 months, 6 months, 1 year, 1.5 years, 2 years and every year until 7 years and then every other year post transplant) to evaluate for rejection of the heart allograft and guide changes in immunosuppression. Unscheduled biopsies of either organ were performed whenever clinical noninvasive testing suggested allograft dysfunction. Kidney biopsies were graded by the updated Banff criteria[15,16] and endomyocardial biopsies were scored by the ISHLT grading system [17]. Echocardiographic examination and renal ultrasound were performed at the time of endomyocardial and renal biopsies, respectively.

Routine DSA screening was performed weekly for the first month, monthly for the first year then quarterly thereafter, for any change in clinical status, and /or for suspicion of medication non-adherence (MNA) using single HLA class I and class II Luminex multibead arrays as previously described[14,18]. MFI>1000 was considered positive for HLA-A, -B, -DR, -DQ, and ≥2000 for HLA-C and –DP[14,18]. Non-adherence was defined as physician and/or clinic staff documentation of patient reported MNA, undetectable drug levels, or missed appointments [10]. All patients with *de novo* DSA underwent renal and endomyocardial biopsies. Non-HLA antibodies including endothelial cell cross match (ECXM) and anti-MHC class I related chain A antibodies (MICA) were measured if clinically indicated[19]. Non-HLA antibodies have been associated with AMR and delayed graft function[20-22].

Valganciclovir and sulfamethoxazole/trimethoprim prophylaxis was continued for 1 year post-transplantation. BK virus, Cytomegalovirus, and Epstein-Barr virus PCR were monitored monthly for the first year then quarterly thereafter. The estimated GFR (eGFR) is reported as a measure of renal function and was calculated using the updated Schwartz equation for all post-transplant measurements[23]. Serum creatinine concentration was measured using the enzymatic assay. Delayed graft function (DGF) is defined by the requirement of renal replacement therapy within the first week post kidney transplantation.

Results

The demographics are shown in Table 1. Mean age at time of sHKTx was 13.7 years with four males and three females. Three (42.9%) sHKTx patients required dialysis prior to transplant. Six (85.7%) were re-graft patients of either the kidney or the heart. Two (28.6%) patients had a primary kidney disease requiring transplantation (renal dysplasia and renal agenesis, respectively). Of the five remaining patients with secondary causes of renal failure, three (43%) had cardiorenal syndrome (CRS) while two (28.6%) had calcineurin inhibitor (CNI) toxicity. The two patients with CNI toxicity were switched to an mTOR inhibitor and low dose CNI based regimen with minimal improvement and eventually progressed to ESRD. The four cardiac re-graft patients all developed progressive cardiac allograft vasculopathy more than 10 years after their first heart transplant.

Table 2 demonstrates the pre-operative transplant characteristics of the cohort. All patients had significant heart and kidney failure prior to dual listing for sHKTx (Table 2). Two patients had an eGFR ~45 ml/min/1.73m^2 and the remaining five patients had either CKD stage 4- 5[24] or ESRD requiring dialysis. Ejection fraction of the left ventricle at time of transplant ranged from 10-54% (Table 2). While on the waiting list, four of seven patients required inotropic support. One patient required an automatic implantable cardioverter-defibrillator (AICD) while another patient required left ventricular assist device (LVAD) placement both 1 month before transplantation. Additionally, one patient required a dual chamber pacemaker 2 years prior to transplantation. The average waiting time on the United Network for Organ Sharing (UNOS) waiting list was 8.9 months (Table 2).

Notably, there were no perioperative cardiac complications in the cohort. Renal complications including acute tubular necrosis (ATN) or delayed graft function (DGF) developed in two (29%) patients (Table 2). One patient required diuretics for ATN management. The other patient had DGF secondary to biopsy proven ATN and required continuous veno-venous hemodialysis (CVVHD) initiated on post-operative day (POD)#0 until his death on POD#30. This patient had VACTERL association (vertebral defects, anal atresia, cardiac defects, tracheo-esophageal fistula, renal anomalies, and limb abnormalities) and his first renal allograft failed after 10 years secondary to CNI toxicity and chronic urinary tract infections. This patient's heart failure was due to complex congenital heart disease with failed Fontan palliation that resulted in ascites and hepatic fibrosis. Because of early ATN, a renal sparing induction protocol was used. Daclizumab was selected in lieu of ATG due to concern for a recently treated invasive fungal infection. He eventually died from overwhelming sepsis and acute respiratory distress syndrome (ARDS) (Table 3).

The post-operative transplant characteristics are shown in Table 3. The most recent outpatient blood pressure and degree of proteinuria measured from urinalysis are shown. Since all of the patients except for patient 6 are >18 years, the guidelines from the American Heart Association (AHA) were used to categorize the hypertension. Renal pathology from the most recent protocol biopsy is shown. Patients 2 and 6 did not undergo protocol biopsies since they were transitioned to the adult kidney transplant program at their home medical center within 6 months after transplantation. Patient 7 expired within 1 month and thus protocol biopsies were not performed.

Overall, short-term outcomes including 1-year patient and sHKTx graft survival in the cohort were 85.7% and 85.7%, respectively. 3-year patient and sHKTx graft survival continued to be consistent at 85.7% and 85.7%. The remaining six patients had considerable improvement in renal and cardiac function post-transplantation with good long-term allograft function (Figures A&B). All are alive with adequate heart and kidney graft function at 2-14 years post-transplantation.

Table 4 displays the immunological characteristics, rejection episodes and corresponding treatment of the cohort. Non-HLA antibodies including endothelial cell cross match (ECXM) and anti-MHC class I related chain A antibodies (MICA) were measured in one patient with evidence of antibody mediated rejection (AMR) on biopsy without detectable HLA antibodies. Four patients (57.1%) were sensitized to HLA antigens with cPRA>50% prior to transplantation [25]. Four patients (57.1%) who had known preformed HLA DSA received pre-transplant desensitization and underwent transplantation after successfully reaching the goal thresholds for both B and T cell crossmatches. T cell complement dependent cytotoxicity (CDC), and B cell CDC crossmatches were negative for all four patients. Patient 2 required her 2nd heart transplant for lifesaving measures so the decision was made to proceed with sHKTx despite positive DSA to B44 (MFI: 1625) and DQ5 (MFI: 3115) with a negative T flow crossmatch and a positive B flow crossmatch of 132 MCS after pronase. Neither B44 nor DQ5 were repeat mismatches from her previous transplant. B44 resolved immediately after transplant, while DQ5 persisted. The patient was treated with monthly IVIG for 7 months resulting in a significant reduction of DQ5 DSA (MFI: 1300) and, stable kidney function (GFR range 75-90 ml/min/1.73m^2) without any evidence of biopsy proven acute rejection. Patient 5 was transplanted through a preformed HLA DSA to DR1 (MFI: 1700) with negative T and B pronase crossmatch. DR1 was not a repeat mismatch from the previous transplant and resolved after transplantation with IVIG for 5 doses. Patient 7 was treated with plasmapheresis and IVIG prior to his 2nd kidney transplant with HLA DSA DR17 (MFI: 4000). DR17 was not a repeat mismatch from the previous transplant and resolved immediately after the transplantation. Patient 6 was transplanted with preformed DSA to DP402 (MFI: 2214) with negative T and B pronase crossmatch. The patient also developed *de novo* DSA (DR52: 3904 MFI; DR4:3284 MFI) without rejection due to under immunosuppression early in the post-operative course and was successfully treated with IVIG × 3 doses. The patient only received immunosuppression with solumedrol and tacrolimus secondary to sepsis from Pseudomonas aeruginosa and Vancomycin-resistant Enterococci. The remaining three patients had negative CDC and flow crossmatch transplants without DSA.

Overall, 14% (1/7) had biopsy proven kidney transplant rejection, while no patients had clinically significant biopsy proven cardiac rejection > 1R/1A. Patient 1 exhibited recurrent kidney transplant acute cellular rejection (ACR) and AMR episodes associated with *de novo* anti-endothelial antibody with no HLA or MICA DSA. The patient had known MNA and was treated with pulse intravenous methylprednisolone, IVIG, rituximab and plasmapheresis.

Discussion

To date, this is the largest case series for pediatric sHKTx describing clinical management, complications and outcomes of a largely sensitized, HLA mismatched, re-transplant population. Although the 1 and 3 year patient survival was 85.7% and 85.7%, the surviving 6 patients enjoyed excellent 3 year allograft survival of 100%. Given the paucity of information in the literature for pediatric sHKTx, our case series highlights the ability to transplant complicated sHKTx patients with enhanced immunosuppression and careful post-transplant monitoring.

In our cohort the main indication for sHKTx was hypoperfusion to the kidney secondary to repeated episodes of sepsis and/or nephrotoxic medications from a previous heart transplant. This reflects the changing nature of simultaneous transplantation of combined end stage heart and kidney failure. VACTERL association and syndromes that encompass defects in both kidney and heart function are no longer primary indications for sHKTx. Instead, advances in both immunosuppressive regimens and surgical techniques have led to improved post-transplant survival of patients with isolated kidney or heart transplant. Consequently, the population of patients requiring combined organ re-transplantation has increased, and these patients are more likely to be sensitized. Evaluating the management and associated outcomes of these high-risk patients is of critical importance.

Our short and long-term outcomes were good despite poor kidney and heart function prior to transplant and the complexity of the recipients in comparison to sensitized pediatric cardiac patients. Jacobs et al reported thirty-day mortality of 25% for their cohort of highly sensitized cardiac transplant patients and Pollock-BarZiv et al described 1-year patient survival of 71% in their high-risk cardiac recipients[6,8]. By contrast, our predominantly sensitized sHKTx cohort had 1-year patient survival of 85.7%. Three highly sensitized patients were successfully transplanted through positive Class II DSAs with low MFIs, which may increase the risk of antibody mediated rejection and graft loss[26]. These patients received enhanced perioperative and post-operative immunosuppression followed by frequent antibody monitoring. These promising results are consistent with Jacobs et al where aggressive desensitization based upon MFI titers and frequent monitoring resulted in 100% 1-year patient survival[25]. Despite transplanting a predominantly sensitized population, our intensive monitoring protocol and timely intervention resulted in no allograft losses from rejection. In fact, our surviving six patients continue to have functioning allografts and have not required re-transplantation, with mean follow up time of 80 months.

The one death in our cohort (patient 7) occurred in a complex VACTERL patient with a previous fungal infection who was induced with daclizumab in an attempt to minimize infectious complications. This patient died approximately 1 month after sHKTx from overwhelming sepsis. Daclizumab is a humanized monoclonal antibody against the interleukin-2 (IL-2) receptor that has been used successfully for induction immunosuppression in kidney transplantation with minimal side effects[27]. However for cardiac transplantation, daclizumab has been associated with an increased risk of overwhelming infection leading to death, which is consistent with our experience [28]. This

data was not published when the decision was made to use it in our patient. Thus, we recommend using anti-thymocyte globulin induction therapy for sHKTx.

Risk factors for morbidity and mortality have not been studied in pediatric sHKTx. We found that the use of daclizumab was the sole risk factor for mortality in pediatric sHKTx. Traditional risk factors associated with increase morbidity and mortality in adult sHKTx such as dialysis and pre-transplant need of a ventricular assist device were not major factors in our pediatric cohort. By contrast, using UNOS data, Russo et al. found that risk factors for diminished survival in adult sHKTx included patients >65 years at time of transplant, peripheral vascular disease, non-ischemic etiology of heart failure, dialysis dependence at time of transplantation and those who required using a ventricular assist device as a bridge to transplantation[29]. However, Russo et al did not address the issue of sensitization. We found that neither cPRA >50% or low level preformed antibody were associated with allograft loss or death. Additionally, our patient with multiple recurrent kidney allograft rejection episodes from MNA has not had any episodes of cardiac rejection. This possible "protective effect" of a single allograft in comparison to multiorgan co-transplants of liver, kidney and heart allografts has been previously demonstrated[30]. Our study is consistent with previous studies in the adult population and supports the idea that sHKTx patients have decreased long term morbidity, including decreased number of heart rejection episodes, and decreased development of cardiac allograft vasculopathy, possibly through immunologic tolerance[31-34].

In the pediatric population, the rate of development of ESRD following isolated pediatric heart transplantation is between1-3%[35,36]. The threshold eGFR for performing sHKTx versus isolated cardiac transplant has not yet been established in pediatrics, and the data in the adult population is limited. Recently, Karamlou et al studied 25,590 isolated heart transplant adult patients and 593 sHKTx recipients from the UNOS dataset ranging from 2000-2010. This group found that early renal failure requiring renal replacement therapy was approximately 10% among isolated heart transplant recipients especially in individuals with an eGFR <37 ml/min/.173m^2 [37]. Raichlin et al showed that 44% of their 19 isolated adult heart transplant recipients with eGFR <40 ml/min/1.73m^2 developed ESRD within 3 years[38]. Additionally, an eGFR <50 ml/min/1.73m^2 prior to isolated adult cardiac transplant has also been associated with a doubling of 30-day mortality[39]. This would suggest that for high risk children with chronic failing heart and kidneys, who are predominantly sensitized, such as in our cohort, an eGFR cut-off of <50 ml/min/1.73 m^2 may be reasonable. Schaffer et al in 2013 found that 5 year post-transplant survival was improved in sHKTx adult patients versus isolated heart transplant recipients, regardless of dialysis status[40]. Furthermore, preemptive kidney transplantation has been associated with improved long-term patient and renal allograft survival[41-43]. However, native kidney function must be optimized prior to transplant given the current shortage of organs as patient with CKD stage 3 can be maintained with stable renal function for several years. CNI sparing regimens should be instituted prior to significant eGFR decline. This is highlighted by the fact that our 2 patients with moderate/severe CKD stage 3 progressed to ESRD despite conversion to a CNI minimization regimen. Some providers might advocate staging heart and kidney transplantation by offering isolated heart transplant recipients to stable CKD stage 3 patients and only proceeding with kidney transplantation for patients with CKD stage 4 and/or

ESRD. Pediatric patients with kidney after heart transplantation have good clinical outcomes, with a >90% survival rate at 1-and 5-years. [44]

In conclusion, successful patient and allograft outcomes were attained with frequent monitoring and immediate intervention in our case series of predominantly sensitized patients. We recognize the limitations of our study including retrospective nature, varying induction therapies, and small sample size. Nonetheless, given the scarcity of data in the literature, this single institution experience with high risk pediatric patients can offer potential guidance regarding indication, management, and long-term outcomes for sHKTx.

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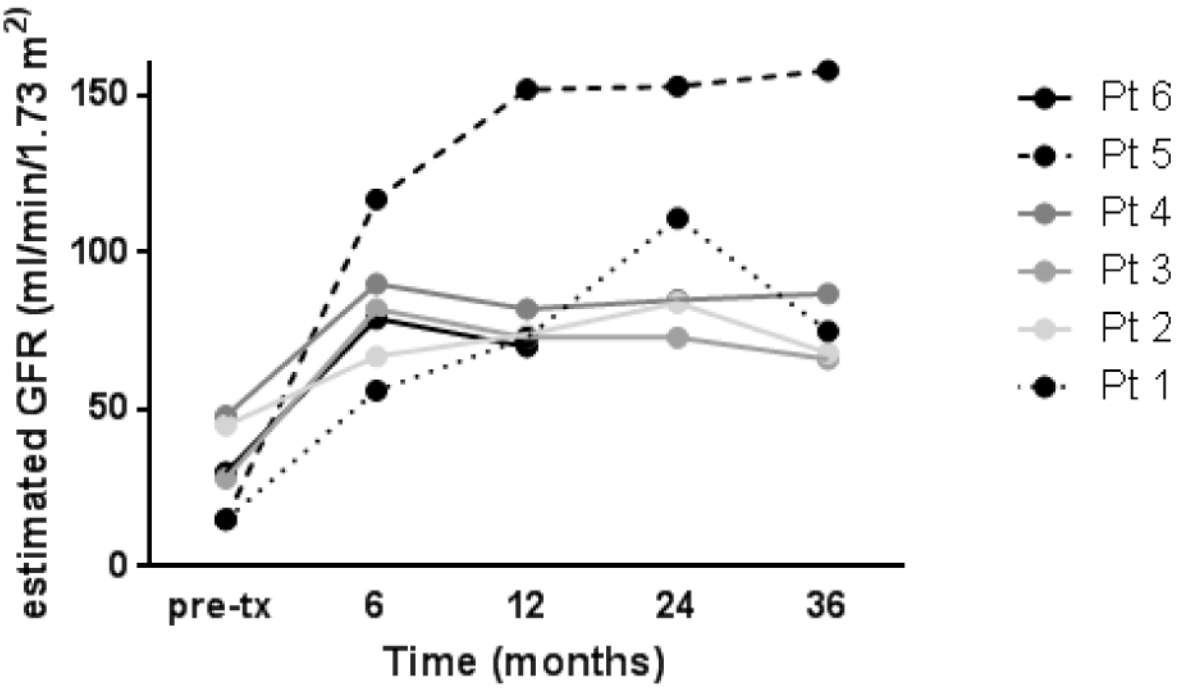

Figure A. Long term renal allograft function (n=6)

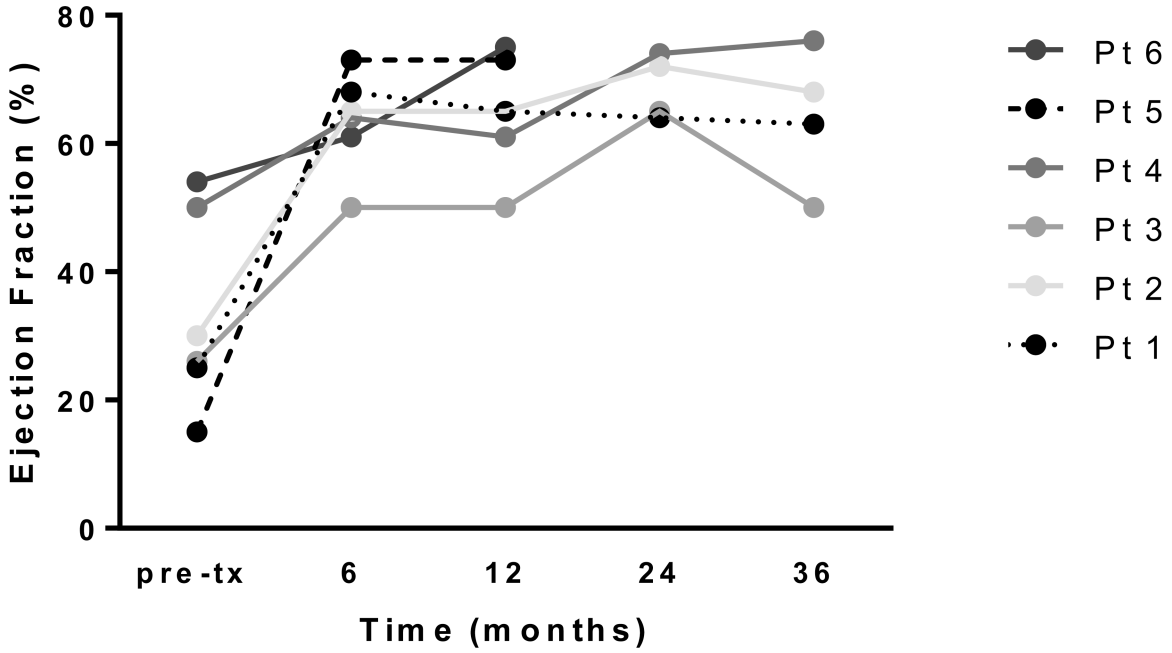

Figure B. Long term cardiac allograft function (n=6)

Table 1

Demographics

N	Age(yr)/Gender	Race	Ethnicity	Previous TX	Primary Diagnosis	Secondary Diagnosis
1	9.8/F	Caucasian	Latino	Kidney	Renal dysplasia, allograft nephrectomy POD #1 secondary to RVT	Dilated cardiomyopathy secondary to stage D heart failure
2	20.9/F	Caucasian	Latino	Heart	DILV and post OHT CAV	CNI toxicity
3	17/F	Caucasian	Not Latino	Heart	Dilated cardiomyopathy and post OHT CAV	CRS
4	16.4/M	Caucasian	Latino	Heart	HLHS and post OHT CAV with progression to stage D heart failure	CRS
5	11.5/M	Black	Not Latino	Heart	HLHS and post OHT CAV with progression to stage D heart failure	CNI toxicity
6	4.3/M	Caucasian	Not Latino	No	Right dominant AV canal, hypoplastic aortic arch with coarctation; s/p extracardiac Fontan	CRS
7	15.8/M	Caucasian	Latino	Kidney	VACTERL, renal dysplasia, post KT reflux nephropathy, contrast nephropathy, CRS	DORV, s/p failed Fontan procedure

TX, transplant; RVT, renal vein thrombosis; DILV, double inlet left ventricle; OHT, orthotopic heart transplant; CAV, cardiac allograft vasculopathy; CNI, calcineurin inhibitor; CRS, cardiorenal syndrome; HLHS, hypoplastic left heart syndrome; KT, kidney transplant; DORV, double outlet right ventricle

Table 2

Pre- Transplant Characteristics

N	Pre-TX Dialysis/GFR *	Pre-TX EF	SHKTx Date	Wait time (months)	DGF
1	PD/<15	20-25%	7/30/2002	15	no
2	no/30	54%	9/17/2014	25	no
3	no/45	30%	3/11/2007	5	no
4	no/28	26%	10/5/2007	0.5	no
5	no/48	50%	1/6/2010	5	no
6	PD,HD/<15	10-15%	8/14/2010	10	no
7	HD/<15	40%	2/26/2004	2	yes

TX, transplant; GFR, glomerular filtration rate; SHKTx, Simultaneous Kidney Heart Transplant; DGF, delayed graft function; PD, peritoneal dialysis; HD, hemodialysis

*Measured in ml/min/1.73m^2

Table 3

Post-Operative Transplant Characteristics

N	Blood Pressure*	Hypertension Stage*	Proteinuria**	Most recent renal pathology	Current eGFR	Current EF	Follow up (months)	Current Status
1	119/79	Normal	30-100 mg/dl	CTG; >50% IFTA	33	63%	156	Alive
2	157/86	Stage 1	100 mg/dl	None	78	60-65%	7	Alive
3	130/82	Prehypertension	Negative	No ACR/AMR, no chronic tubulointerstitial changes	76	50-55%	102	Alive
4	125/74	Prehypertension	Negative	No ACR/AMR, no chronic tubulointerstitial changes	108	61%	95	Alive
5	110/68	Normal	Negative	No ACR/AMR, no chronic tubulointerstitial changes	66	60%	57	Alive
6	122/60	Prehypertension	Negative	None	170	61%	3	Alive
7	NA	NA	NA	NA	NA	NA	1	Deceased

*oscillometric reading from most recent outpatient appointment, guidelines recommended by American Heart Asssociation except for patient 6, guidelines based on 4th report on the Diagnosis, Evaluation and Treatment of High Blood Pressure in Children and Adolescents, 2004, *Pediatrics* 114:555-5767

**Proteinuria on most recent outpatient urinalysis

eGFR, estimated glomerular filtration rate; EF, ejection fraction; CTG, chronic transplant glomerulopathy; IFTA, interstitial fibrosis and tubular atrophy; NA, not applicable; ACR, acute cellular rejection; AMR, antibody mediated rejection

Table 4

Immunological Characteristics, Allograft Rejection, and Treatment

N	cPRA	HLA MM	IS	Rejection pathology	Rejection treatment	DSA	Effect of treatment on DSA
1	50%	1A, 1B, 2DR,0DQ	Solumedrol MMF tacrolimus	Kidney ACR 1A 2007, 2009, 2010, 2013; AMR 2011	ACR: steroids(2007, 2009, 2010, 2013), IVIG (2013); AMR: steroids, IVIG, PP, rituximab	None, +endothelial cell antibody in 2011, *de novo* post-transplant	Persistent +Endothelial cell antibody
2	88%	2A,1B, 1DR,1DQ	ATG solumedrol MMF tacrolimus	Heart ACR 1R 2015 -no cardiac dysfunction	Did not require treatment	HLA B44 (MFI 1625),DQ5 (MFI 3115), preformed pre-transplant	B44 resolved, DQ5 significantly reduced
3	0%	2A, 2B, 1DR, 1DQ	ATG solumedrolMMF tacrolimus	None	NA	None	NA
4	0%	2A, 1B, 2DR, 1DQ	ATG solumedrol MMF tacrolimus	Heart ACR 1R 2008 – no cardiac dysfunction	Did not require treatment	None	NA
5	97%	2A, 2B, 1DR, 1DQ	ATG solumedrol MMF tacrolimus	None - asymptomatic	IVIG for +DSA and elevated BNP	HLA DR1 (MFI 1700) preformed pre-transplant	DR1 resolved
6	19%	1A,2B, 2DR,2DQ	ATG solumedrol MMF tacrolimus	None	IVIG for +DSA, no rejection on biopsy	HLA DP402 (MFI 2214), preformed HLA DR52 (MFI 3904), DR4(MFI 3284*), de novo* post-transplant	DP402, resolved DR 52, resolved DR 4, resolved
7	67%	1A,2B, 2DR,0DQ	Daclizumab solumedrol MMF tacrolimus	None	NA	DR17 (MFI 4000) Preformed Pre-transplant	DR17, resolved

cPRA, calculated panel reactive antibody; MM, mismatch; IS, Immunosuppression; DSA, donor specific antibody; MMF, mycophenolate mofetil; ACR, acute cellular rejection; AMR, antibody mediated rejection; IVIG, intravenous immunoglobulin; PP, plasmapheresis; ATG, anti-thymocyte globulin; NA, not applicable