



Heart transplantation for patients with single ventricle physiology

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Received: 8 January 2021 / Revised: 12 July 2021 / Accepted: 13 July 2021 / Published online: 7 October 2021
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Abstract

Background There is a growing population of palliated and unpalliated single ventricle physiology patients for whom heart transplantation is the only treatment option available. There is a paucity of reports of heart transplantation in this challenging and growing subset of patients from our part of the world. The purpose of the article is to briefly review our experience in the subgroup and compare it with the available literature.

Methods This was a single-institution retrospective observational study of 16 patients with single ventricle physiology who were transplanted between 2016 and 2019 and their outcomes. The study groups were divided into those with ventricular dysfunction (group 1), who fare substantially better than those with normal ventricular function (group 2) whose short-term outcomes were poorer. Worsening cyanosis, poor candidacy for completion Fontan procedure due to severe atrioventricular valve regurgitation or pulmonary artery anatomy, protein-losing enteropathy, plastic bronchitis, and worsening systemic venous congestion are indications in those with normal ventricular function.

Results Patients with ventricular dysfunction as the main indication had excellent early survival with no early mortality compared to 40% mortality in patients with normal ventricular function. Patients who survived to leave the hospital had however similar long-term outcomes. Two patients with protein-losing enteropathy resolved completely by one month. Normal ventricular function, pulmonary artery stenting, early Fontan failure (6 months), ascites, and need for desensitization were risk factors for early mortality. After the early acute phase of increased risk, the mortality risk plateaued off.

Conclusion Transplantation in patients with single ventricle and ventricular dysfunction can be offered with a good early and late outcome. There is a need to have multi-institutional and multi-disciplinary collaboration along with work in basic sciences to better understand the effects of failed Fontan physiology with normal ventricular function.

Keywords Congenital heart disease · Single ventricle physiology · Cardiac transplantation

Introduction

Single ventricle patients can be broadly categorized into those with reduced systemic flow and those with reduced pulmonary flow. The hypoplastic left heart and its variants would come under the reduced systemic flow category. The initial management and stabilization of this subset are clinically challenging and would need a Norwood I type palliation, which essentially means amalgamation of systemic and pulmonary flows and using a controlled pulmonary flow in the form of systemic to pulmonary artery (PA) shunt or right ventricle (RV) to PA shunt or conduit or some type of PA banding.

Staged palliation of children born with single ventricle physiology has benefited a significant number of children. Stage I involves providing unimpeded systemic flow and

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controlled pulmonary blood flow, stage II involves superior cavopulmonary connection and stage III is total cavopulmonary connection achieving separation of systemic and pulmonary circulation. Various procedures may be added to these basic procedures depending on the individual anatomy and physiology. Heart transplantation is considered the stage IV single ventricle palliation and according to conservative estimates, 30–40% of children born with single ventricle physiology would become eligible for heart transplantation. This subgroup is the most rapidly raising diagnostic group and also perhaps the most complex cohort presenting to the heart transplant team.

With only 47% freedom from composite morbidity at 20 years, much work remains to improve the quality and longevity of life in these patients [1, 2].

Aim of the study

The aim of this study was to evaluate our institutional experience in single ventricle patients undergoing heart transplant, review the current literature, and discuss the various challenges encountered and the lessons learnt.

Methodology

This was a single-institution retrospective observational study of 16 patients with single ventricle physiology who underwent heart transplant between 2016 and 2019. There were 9 males and 7 females. The mean (\pm standard deviation) age at the time of transplantation was 16.37 ± 9.6 , range 6 years to 44 years. The follow-up period ended in November 2020. Informed consent was taken from all patients for utilization of their data and Institutional Ethics Committee approval was duly sought.

Study groups

The patients were divided into two groups—those with ventricular dysfunction (group 1) and \pm those with normal ventricular function (group 2). Many parameters were collected and compared between the two groups. These included gender, age at transplantation, INTERMACS (Interagency Registry for Mechanically Assisted Circulatory Support), and wait-list duration. The post-transplantation variables were donor-recipient weight ratio, donor heart ischemia time, cardiopulmonary bypass time, hospital stay post-transplantation, and patient survival.

Indications for heart transplant

The primary indication for transplant was severe ventricular dysfunction. In patients with normal ventricular function, worsening cyanosis, poor candidacy for completion Fontan

procedure due to severe atrioventricular valve regurgitation or PA anatomy, protein-losing enteropathy (PLE), plastic bronchitis, and worsening systemic venous congestion were the indications.

Eligibility criteria

Inclusion criteria

Males and females who had undergone heart transplantation for complications of congenital single ventricle heart. With or without previous palliations

Exclusion criteria

Pediatric patients who underwent heart transplantation for cardiomyopathy
 Patients with signs of infection at the time of transplantation
 Patients with signs of neurological injury
 Patients with renal function disorders or anuria or chronic renal failure
 Patients with severe metabolic abnormalities
 Patients with genetic syndromes
 Patients with pulmonary vascular resistance (PVR) more than 6 units Wood/m²

Outcome measures

Primary outcomes are early and late survival and mortality of patients among both groups.

Secondary outcomes are cardiopulmonary bypass time and hospital stay in both groups.

Statistical analysis

A descriptive analysis of the data collected from the 16 patients was performed that included demographic data and clinical outcome. Survival analysis was done by determining the actuarial survival curve, derived by the Kaplan-Meier method. Descriptive statistics include the mean \pm standard deviation for continuous variables and frequencies for categorical variables. Continuous variables were compared between patients with and without ventricular dysfunction (groups 1 and 2) by unpaired t test. The chi-square analysis was used to compare discrete variables. A $p < 0.05$ was considered significant. Data were analyzed using the SPSS software, Version 26 (SPSS Inc., Chicago, IL, USA).

Results

A total of 257 patients underwent heart transplantation at our center from October 2012 to October 2019. Ninety-seven were the number of pediatric patients less than 18 years. In total, 11.3% (11/97) of patients had congenital heart disease as an indication for transplant, compared to 10% ((16/160) in adults. Though dilated cardiomyopathy predominated as the most common indication, the percentage of patients with congenital heart disease requiring transplantation was likely to be increased in both the adult and pediatric population. Among the pediatric heart transplant patients, only one patient was on mechanical support and one was admitted requiring inotropes. The others were in INTERMACS 5 or 6 or New York Heart Association (NYHA) class IV with medical therapy. The wait-list duration ranged from a minimum of 2 weeks to a maximum of 10 months period (mean 3.2 months). Comparison of pre-operative and post-operative variables have been elaborated in Table 1 and Table 2 respectively. Data was represented as mean \pm standard deviation or percentage of patients.

Sixteen patients had heart transplantation for single ventricle physiology and they were the focus of the present manuscript. The early mortality was 25%, 1-year survival was 75%, and 5-year survival was 63%. The survival curve for these patients is given in Graph 1. The surviving patients were in excellent functional class and encouraged us to

Table 1 Comparison of pre-operative variables: Data are represented as mean \pm standard deviation or percentage of patients

| | Group 1 (n = 8) | Group 2 (n = 8) | p value |
|-----------------------------|------------------|-----------------|---------|
| Age (years) | 15.08 \pm 9.71 | 17.8 \pm 9.55 | NS |
| Gender (F/M) (%) | 62.5/37.5 | 75/25 | NS |
| INTERMACS (1, 2, 3, 4) (%) | 12.5/12.5/25/50 | 0/0/25/75 | NS |
| Wait-list duration (months) | 6.8 \pm 1.7 | 5.62 \pm 1.82 | NS |

NS non-significant as *p* value > 0.05

Table 2 Comparison of post-operative variables: Data are represented as mean \pm standard deviation or percentage of patients

| | Group 1 (n = 8) | Group 2 (n = 8) | p value |
|-------------------------------|--------------------|-------------------|---------|
| Donor ischemia time (minutes) | 180.5 \pm 80.92 | 197.62 \pm 83.3 | NS |
| Donor/recipient weight ratio | 2.2 \pm 0.9 | 1.4 \pm 0.91 | NS |
| CPB time (minutes) | 196.12 \pm 62.03 | 256.5 \pm 60.95 | NS |
| Early survival | 100% | 50% | NS |
| Late survival | 87.50% | 37.50% | NS |
| Hospital stay (days) | 22.8 \pm 14.91 | 31.12 \pm 14.49 | NS |
| Follow-up duration (months) | 41 \pm 10.69 | 30.62 \pm 11.84 | NS |

NS non-significant as *p* value > 0.05. Early survival is defined as survival till discharge. Late survival is defined as survival on follow-up

persist with this treatment modality despite its higher initial mortality and the various anatomical, technical, immunological, and financial challenges.

Discussion

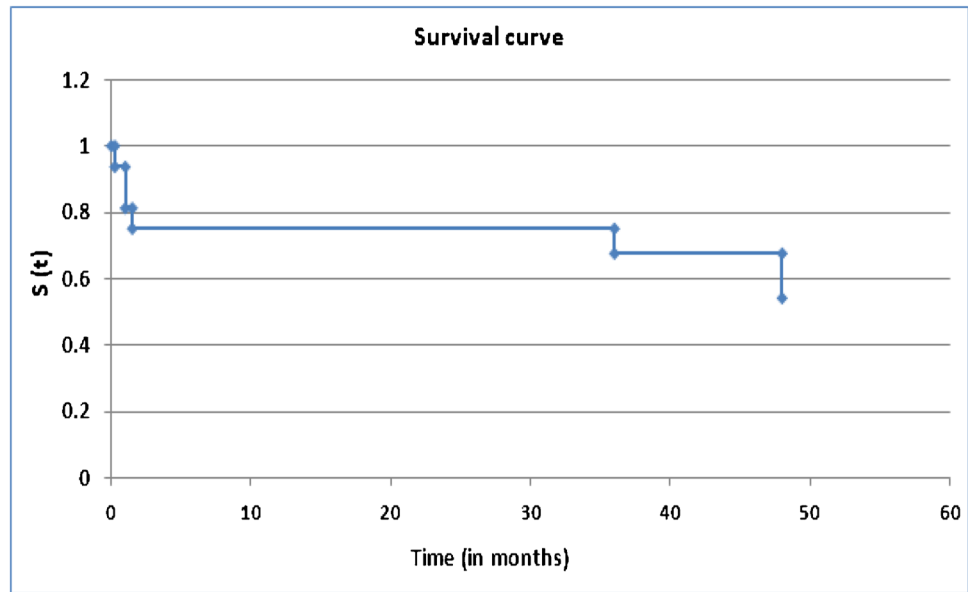
The indication for heart transplantation and mortality

The indication can broadly be defined as those with ventricular dysfunction and those with failed Fontan physiology. The flow chart briefly summarizes our outcome in these two subgroups (Flowchart 1). The decision to transplant in those with ventricular dysfunction is relatively straightforward and the recommendations for the adults and children with cardiomyopathy can be applied in this scenario. The outcomes are also the best with this subset where the indication in ventricular dysfunction. Table 3 summarizes our experience.

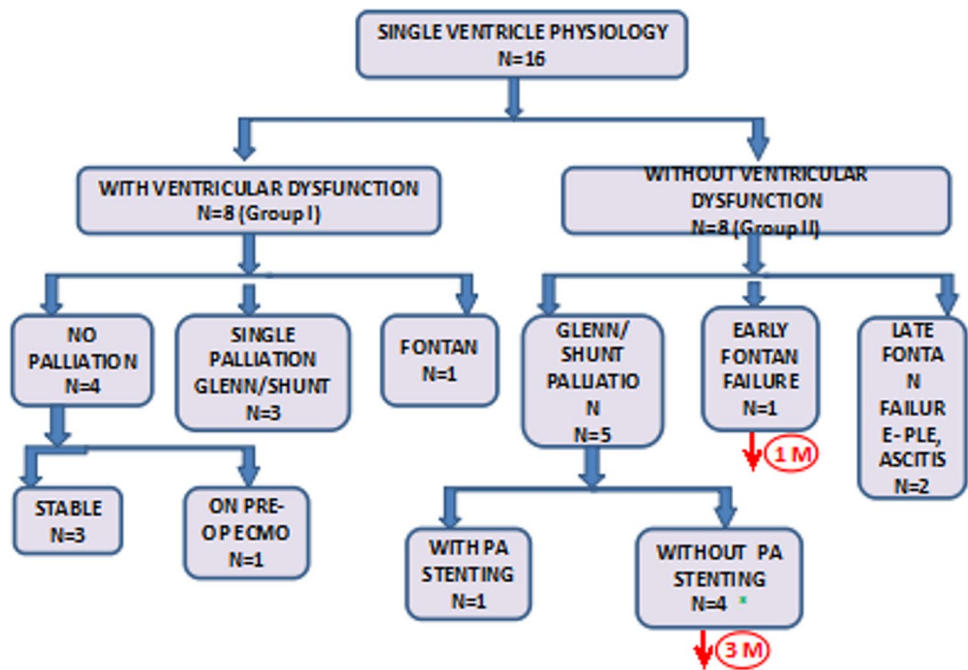
Six patients had ventricular dysfunction (EF < 25%) as the predominant indication and all of them survived. Some of the patients had ventricular dysfunction and protected pulmonary circulation with no previous surgery or only one surgery. These patients form the best cohorts and their early and long-term outcomes are excellent. Of these 5 patients, one of them did not have any previous palliation and had supra-cardiac total anomalous pulmonary venous connection (TAPVC), which was repaired by using the native atrial tissue to anastomose to the opened up common chamber; this was used as the cuff for donor left atrial anastomosis. Two patients had one previous palliation, 2 had 3 previous palliations, one of them had Fontan completion, and one was on mechanical circulatory support, extracorporeal membrane oxygenation (ECMO) at the time of transplantation.

Ten patients had failing single ventricular palliation with normal or only mild dysfunction. The indications were severe cyanosis with functional disability, PLE with increasing albumin requirements, and high venous pressures making them unsuitable for Fontan procedure with worsening cyanosis and ascites with high Fontan pressures with normal

Graph 1 The overall Kaplan–Meier survival curve for the entire group of 16 patients



Flowchart 1 The flowchart depicts the classification of the study group into those with and without ventricular dysfunction. The early mortality in each subset has been marked in red accordingly. The green asterisk in the palliation category denotes a sensitized patient with a positive direct cross match that required de-sensitization



ventricular function. There was 40% early mortality in this subgroup. The indication in this subgroup is unclear and how far medical management with pulmonary vasodilators can postpone transplantation without affecting the end-organ function or outcome is not clear. One unifying feature is that their life is miserable with functional limitation and no further surgical, medical, or “interventional” interventions are possible or are at a very high risk to improve the single ventricle hemodynamics. Graph 2 clearly shows the much better survival post-transplantation of single ventricle

physiology patients with ventricular dysfunction than those with normal function.

Of the transplantation for patients with normal ventricular function, the early Fontan failures are the worst subset. Bidirectional Glenn staging was confirmed as the best bridge to a heart transplant, with 100% 5-year survival after orthotopic heart transplantation (OHT). Early Fontan failure represented the only independent predictor of mortality after OHT, with an odds ratio of 13.1 and a dismal 20% 1-year survival, while excellent outcome (90% 5-year survival) in OHT candidates for late Fontan failure without significant

Table 3 Experience with 16 patients with single ventricle physiology who underwent cardiac transplantation

| Diagnosis | Age in months Sex | Previous palliations | Date of surgery | Remarks |
|---|----------------------|---|-----------------|--|
| Mitral atresia, hypoplastic LV, DORV, severe PS, supra-cardiac TAPVC, ventricular dysfunction | 12 F | None | 13–5-16 | Common chamber augmented with right atrial tissue before implantation, smooth postoperative course, doing very well |
| DORV, non-routable VSD, severe AV valve regurgitation, severe ventricular dysfunction | 12 M | BT shunt BD Glenn with MPA interruption | 4–6-16 | Small LSVC which was ligated, due to the presence of connecting vein had increased secretions from left bronchus, needed re-intubation improved with conservative management, doing well |
| DORV, large remote VSD, PS, RPA replaced by a leash of collaterals, kyphoscoliosis | 19 M | Right BT shunt, Left BT shunt, BD Glenn with MPA interruption | 18–10-16 | Heart transplant to single left lung, PFO left open, discharged after one month with room air saturation of 90 s, good quality life for 4 years, passed away during brief respiratory illness |
| DORV, Severe PS, side by side great arteries, attempted bi-ventricular repair, taken down to single ventricle | 6 M | BT shunt BDG with MPA interruption, LV aneurysm repair | 18–11-16 | Doing very well, relatively uneventful recovery |
| Single ventricle, S/P Fontan with Norwood modification, severe protein-losing enteropathy | 23 m | S/P fenestration creation, s/p Device closure of fenestration | 8–1-17 | Married post-transplant, doing well, resolution of PLE |
| ccTGA, VSD PS, biventricular dysfunction, aneurysmal dilation of Glenn anastomosis | 44 M | S/p Bidirectional Glenn surgery | 21–3-17 | Had Glenn anastomosis give way post-transplantation, SVC reconstructed with bovine pericardium under circulatory arrest, relatively uneventful recovery, doing well |
| Tricuspid Atresia, Severe PS, TGA, severe ventricular dysfunction | 12 F | Was on ECMO before surgery for 3 weeks | 4–9-17 | Recovered well, had a good quality of life for 30 months, passed away during the pandemic due to Miliary TB and COVID -19 positivity |
| Mitral Atresia, Hypoplastic LV, DORV, severe PS, AV valve regurgitation, ventricular dysfunction | 18 F | Left BT shunt | 5–9-17 | Left shunt, clipped and divided, uneventful recovery, doing well |
| Common AV canal, common AV valve, severe regurgitation, hypoplastic RV, ventricular dysfunction, LSVC | 7 years F | No previous palliation | 28–10-17 | PTFE used for LSVC to RA continuity, uneventful recovery, doing well |
| DILV, DORV, Hypoplastic LV, Dilated common atrium, common AV valve, severe AV valve regurgitation, Atrial arrhythmia, Interrupted IVC with Hemiazygous continuation | 21 F | Left Kawashima repair | 12–3-18 | PTFE tube used to establish continuity with left Kawashima and donor right atrium, Initial postop period uneventful, shifted toward developed liver dysfunction, unexplained neurological worsening, RV dysfunction, passed away at 32-day post-transplant |
| S/P Fontan for single ventricle PS with failed early Fontan physiology with gross ascites and hypoalbuminemia | 8 years F | S/P Glenn, S/p LPA stenting for LPA origin narrowing | 27–7-18 | Early Mortality, due to donor mismatch, severe adhesions, uncontrolled bleeding, extremely friable PA and LA tissues |
| Unbalanced AV canal severe AV valve regurgitation single ventricle of RV morphology, common atrium, situs ambiguous, hepatic veins opening separately bilateral SVC | 17 F | No previous palliation | 18–8-18 | Separate hepatic veins baffled to the right side by using atrial tissue, innominate vein used for suturing to LSVC, uneventful recovery, doing well |

Table 3 (continued)

| Diagnosis | Age in months Sex | Previous palliations | Date of surgery | Remarks |
|---|----------------------|--|-----------------|--|
| Unbalanced AV canal, moderated AV valve regurgitation, DORV, VSD, PS, severe cyanosis | 25 M | S/p Glenn with central shunt, S/p LPA, stent placement | 19–9–18 | Mortality at 45 days, gradual onset RV dysfunction, sepsis, renal dysfunction, and multiorgan failure |
| Tricuspid atresia, PS, S/P Fontan with severe protein-losing enteropathy | 16 M | s/p right BT shunt, S/P BDG, and Fontan | 14–2–19 | Protein-losing enteropathy resolved, delayed dehiscence of femoral cannulation site, requiring local rotation flap, 2 episodes of rejection requiring pulse steroids with good response, currently in good clinical status |
| S/P Fontan procedure, tricuspid atresia, severe ventricular dysfunction | 8 years F | S/p BDG and S/p Fontan | 1–7–19 | Uneventful postoperative recovery, doing well |
| cTGA, DILV, hypoplastic RV | 14 years M | s/p PA banding and atrial septectomy, S/P DKS procedure, and Glenn, S/p Fontan | 3–7–19 | Needed desensitization preop due to positive direct cross match, post-op developed worsening RV dysfunction, sepsis, passed away at 30 days |

DORV double outlet right ventricle, PS pulmonary stenosis, TAPVC total anomalous pulmonary venous connection, VSD ventricular septal defect, BT Blalock-Taussig, BDG bidirectional Glenn, LSVC left superior vena cava, MPA main pulmonary artery, RPA right pulmonary artery, LPA left pulmonary artery, PFO patent foramen ovale, PLE protein-losing enteropathy, ccTGA congenitally corrected transposition of great arteries, ECMO extracorporeal membrane oxygenator, PTFE polytetrafluoroethylene, DILV double inlet left ventricle, AV atrioventricular

end-stage comorbidities (hepatic cirrhosis, chronic malnutrition) [2].

Interestingly in two patients, the indication was PLE with very low albumin levels (around 1 g/dl) requiring albumin infusions at increasing frequency. In both patients, the albumin levels returned to normal by 3 weeks post-transplant, and the PLE was cured.

One-year actuarial survival after OHT was 88.9% in impaired ventricular function vs 56.2% in preserved ventricular function [3].

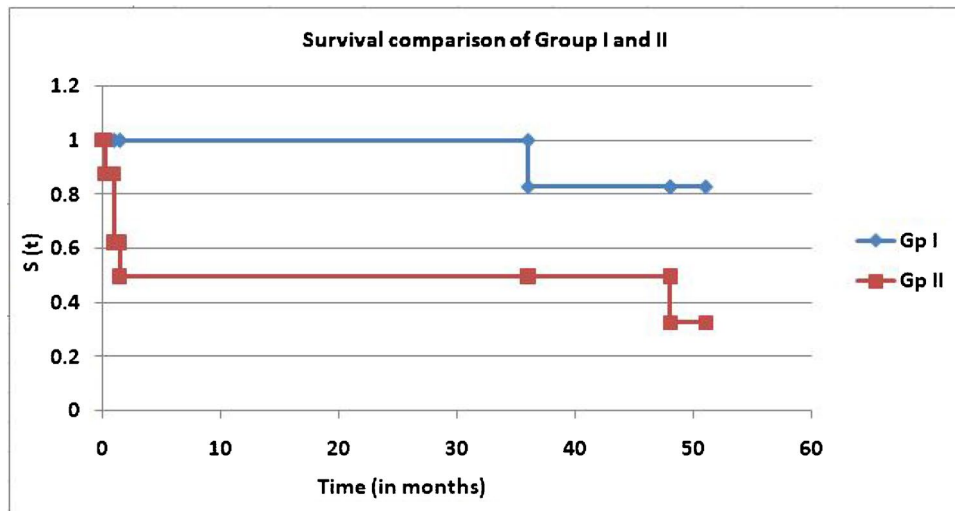
If a patient presents with early Fontan failure with normal ventricular function, the best treatment modality appears to be taking down to Glenn shunt and plan transplantation at a later date. This is however not a low-risk surgery, with a reported mortality risk of around 50% [4].

Jayakumar et al. reported 35 patients with failing single-ventricle undergoing OHT. There were 10 early deaths: 9/10 deaths occurred in the Fontan failure group and only one after Glenn. Seventy percent of the early deaths occurred due to hemorrhage and infections [5].

Patients with normal ventricular function and failed single-ventricle palliation represent a very high-risk subset partly due to our lacunae in understanding the altered “non-physiologic” physiology and indication and contraindication in this subset are likely to evolve as our understanding improves. A high-risk Fontan should be avoided from the Glenn stage, and if there is early Fontan failure, the best bet would still be to the takedown of Fontan to Glenn stage rather than OHT. A mechanical assist device in the Fontan circulation could be an option in this subgroup as a bridge to transplant or as a bridge to recovery. These may reduce the attrition on the waiting list and help bridge the highest risk group of early Fontan failure to successful transplantation.

Panel reactive antibody

This is a test for testing anti-human leukocyte antigen (HLA) antibodies in the recipient serum against common antigens in the population. It is tested against a panel of lymphocytes from approximately 100 blood donors in the local population. Each population has a different demographic prevalence of particular antigen and the panel reactive antibody (PRA) test panel constituents differ from country to country. A purified HLA antigen panel has been used to replace the cell panel for the PRA test, based on the assumption that HLA is the major antigen system in rejection, the effect of non-HLA antibody effect on the PRA has been ignored. Antibodies to class I antigens are considered significant as they are expressed on all cells and T cells, while class II antigens are expressed only on macrophages, dendritic cells, and B lymphocytes. A high PRA value usually means that the individual is primed to react immunologically against



Graph 2 The comparison of Kaplan–Meier survival curves for those with ventricular dysfunction (group I) and those without ventricular dysfunction (group II). Patients with ventricular dysfunction have good early outcomes. One late mortality was due to infection (miliary tuberculosis and coronavirus disease (COVID-19)); the patients without ventricular dysfunction have high early mortality, but after the

increased early hazard phase, their survival is good. One late mortality in this group was in a patient with single lung transplantation who had elevated pulmonary artery pressures and delayed RV dysfunction and passed away suddenly following a brief respiratory illness in the pre-COVID-19 period

a large proportion of the population. A PRA of > 20% is considered significant.

Currently, laboratories use Luminex-based assay for reporting IgG antibodies against class I antigens. Luminex is a solid phase assay where HLA molecules are immobilized on polystyrene microspheres with fluorescent dyes. The patient serum is incubated with microspheres coated with HLA molecules, a second fluorescent antihuman IgG directed against the Fc portion of the antibodies is added, and a laser is used to detect the strength of antibody titer which is reported as mean fluorescence intensity (MFI). Values > 5000 are considered significant [6].

Three patients had significant PRA levels. In two of the patients in whom complement-dependent cytotoxicity (CDC) crossmatch was negative with donor lymphocytes, no desensitization strategies were used. One of them had previous Glenn surgery and the other had previous left-sided systemic PA shunt. The short- and long-term outcomes were good in these patients. One patient had desensitization due to positive crossmatch on two occasions, with rituximab (anti CD 20 monoclonal antibody) which depletes B cells. He was given 2 g on days 7 and 22 and intravenous immunoglobulin (IVIg) (2 g/kg) on days 1 and 30. He then underwent transplantation after 2 weeks, developed sepsis post-transplant, and passed away after 21 days due to a combination of sepsis and right ventricular dysfunction.

Large registry analyses have demonstrated the negative impact of HLA antibodies on patient survival. Desensitization protocols lack proper trials and outcome analysis to support one strategy over the other. Newer biological molecules

like bortezomib (proteasome inhibitor, which depletes plasma cells), eculizumab (complement C5 inhibitor which targets the terminal membrane attack complex), and alemtuzumab (anti CD 52 antibody which depletes leucocytes, macrophages, and monocytes) may alter the strategies to manage desensitization in the future [7].

We have to wait for better understanding, treatment options, and trials in order to deal with the increasing cohort of sensitized recipients. The panel needs to be standardized according to our population. A positive direct crossmatch carries more importance than just the value of PRA. In this small group, PRA values did not carry any immediate or delayed prognostic value or increase in the incidence of rejection.

PVR in Fontan circulation

Surgical and medical techniques have improved our ability to manage patients with deviation from the 10 selection criteria for successful Fontan operation laid down by Choussat in 1977 [8]. The concept of low PVR (anecdotal evidence suggests that < 2 wood units*m² may provide the best long-term outcome rather than 4 wood units*m² as initially suggested) and low mean PA pressure < 15 mm Hg still hold good. The trans-pulmonary gradient may be a better estimate of pulmonary vascular health with trans-pulmonary gradient > 5 mm Hg likely abnormal [9].

The standard definition of pulmonary hypertension of > 20 mmHg mean PA pressure cannot be applied to single ventricle patients, who, even in the presence of florid signs

of Fontan failure, have pressure which is <20 mm Hg. The definition of vasoreactivity is also not applicable to single-ventricle patients.

Determining the optimal PVR and trans-pulmonary gradient remains elusive and accurate calculation of PVR may be difficult. An additional source of pulmonary flow from the native tract, aortopulmonary collaterals, and the presence of decompressing veins contributes to inaccuracies in calculating pulmonary blood flow. Cardiac magnetic resonance imaging (MRI) may provide additional flow data that may help with the calculation of pulmonary blood flow and PVR [10].

Several randomized studies and case series have demonstrated a positive effect of pulmonary vasodilator therapy on exercise performance and in temporary palliation of PLE and plastic bronchitis. Sildenafil, bosentan, ambrisentan, and subcutaneous treprostinil have been tried, with the hope that these can reduce cyanosis and improve exercise tolerance and functional class prior to transplantation. Importantly, bosentan has not been seen to cause an increase in hepatotoxicity, given that the population is at high risk for hepatic dysfunction [11].

A meta-analysis concluded that pulmonary vasodilator therapy improves exercise capacity, hemodynamics, and functional class in Fontan patients. We have yet to determine who would benefit the most and how to determine it in this subset of patients [12].

Early attrition from the single ventricle pathway due to pulmonary vascular disease is better treated with transplantation as PVR in this group is rarely high enough to preclude transplantation. Moreover, long-term outcomes in high-risk Fontan palliation patients remain poor [10].

The reason behind the increase in PVR in Fontan is not completely clear (Table 4) [13–15]. Low cardiac output, excessive hypoxemia, PLE, and plastic bronchitis may all be clinical manifestations of increased PVR after Fontan completion.

All our patients were on pulmonary vasodilators before transplantation. The measurement of PA pressure

post-transplantation was revealing. Transplantation unmasks the high PA resistance which was not allowing the passive blood flow, showing why the Fontan physiology failed in the first place.

All patients who had previous Glenn or Fontan had mean PA pressures of more than 40 in the initial days, which gradually fell to a mean of 25–30 over the course of the week, with simultaneous falling of central venous pressure (CVP) to below 10 mm Hg. Evaluation of patients who did not do well showed a trend of falling PA pressures with raising CVP and falling urine output. These patients have failing RV and aggressive measures to support the RV should be taken. All the patients who survived the operation and had early mortality (4/16) showed this trend at some point in their postoperative period. The patients in whom the PA pressures remain high and the CVP remains low are at higher risk of delayed complications, due to delayed RV failure which was noted in our patient who had transplantation to a single left PA.

PLE and plastic bronchitis

The diagnosis of PLE is mostly clinical in the presence of low albumin with no other explanation of protein loss in a post-Fontan patient. Stool alpha-1 antitrypsin levels and Technetium-99 m-labeled serum albumin scintigraphy is confirmatory but not available in most centers.

The break-in integrity of the enteric mucosal barrier seen in PLE affects a number of homeostatic system's protein loss and leads to reduced vascular oncotic pressure with interstitial and peripheral edema, ascites, pleural and pericardial effusions. Loss of albumin leads to abnormalities in calcium metabolism; loss of coagulation factors further upsets an already abnormal cascade of coagulation. Abnormal flow in lymphatic vessels, as a result of lymphatic engorgement, may lead to chylothorax, lymphopenia, and a relative immunodeficient state [16].

The pathophysiologic mechanism resulting in PLE is still enigmatic but two issues are believed to be involved: lower

Table 4 Possible reasons for elevation of pulmonary vascular resistance post single ventricle palliation

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- Lack of pulsatility or poor pulsatility fails to recruit the distal pulmonary vascular bed
 - Endothelial dysfunction resulting in decreased production of nitric oxide and prostacyclin and increased production of endothelin
 - Increase in lymphatic pressure resulting in reduced distensibility of pulmonary vascular bed and reduced pulmonary compliance
 - Gradual increase in interstitial pressure which caused extra-alveolar blood vessels to decrease in caliber in turn causing blood flow to decrease. (zone 4 of lung where P_i —the interstitial pressure determines the blood flow)
 - Increase in zone 1—area of the lung where alveolar pressure is more than the arterial pressure resulting in the collapse of blood vessels increasing the alveolar dead space
 - Diastolic dysfunction of single ventricle due to chronic lymphatic hypertension impairing passive trans-pulmonary flow
 - Chronic micro thromboembolic events due to loss of anticoagulant factors and sluggish circulation as a result of protein-losing enteropathy
 - Formation of microcasts in the alveoli reducing the area available for gas exchange, resulting in hypoxic vasoconstriction and increased dead space ventilation
-

mesenteric oxygen delivery and inflammation. Patients with PLE after Fontan completion present significantly higher mesenteric vascular impedance and lower mesenteric-to-ceeliac flow ratio than those without PLE. Moreover, the flare of PLE symptoms in Fontan patients frequently occurs after acute viral infections, which implies an inflammatory mechanism. Several studies demonstrated an increase in inflammatory markers in PLE, such as TNF-alpha, C reactive protein, and cytokines which seem to play an important role in altering intestinal cell membrane permeability to intravascular proteins [17].

Management of PLE should encompass the following: (1) symptomatic treatment to relieve edema, correct hypoalbuminemia, and replace lost immunoglobulin and calcium; (2) treatment of congestive heart failure and low cardiac output should be instituted with particular attention to angiotensin-converting enzyme inhibitors, especially in view of findings of high mesenteric vascular resistance; (3) correct anatomic abnormalities such as obstructive lesions in and outside the Fontan circuit and aortopulmonary connections; (4) address intestinal mucosal abnormality with Prednisone and/or Heparin if the other methods do not result in resolution of PLE; and (5) PLE is a potentially fatal disease and should be promptly treated. Cardiac transplantation is an option that should be considered if other measures fail [18].

Patients with plastic bronchitis develop deposits in the airway referred to as casts, which can lead to airway obstruction and respiratory compromise. The clinical presentation is acute and the presentation can be dramatic with rapid worsening. A break in the integrity of bronchial mucosa leads to leakage of proteinaceous material and is probably secondary to lymphatic engorgement. Unlike PLE, hypoalbuminemia may not occur due to the relatively small amount of protein sufficient to cause significant airway obstruction. There are isolated case reports of successful resolution of plastic bronchitis after heart transplantation. Recurrence of plastic bronchitis after transplantation has been reported in the setting of rejection and elevated filling pressures [19, 20].

We do not have a patient with plastic bronchitis in this series. The creation of Fontan fenestration, aerosolized tissue plasminogen activator, steroids, and pulmonary vasodilators (sildenafil and bosentan) have been tried with varying success [21].

In a multicentric study involving 52 patients from 12 centers, with PLE referred for OHT, Schumacher et al. reported resolution of PLE at a median of 1 month in nearly all survivors. They reported that the severity, duration, and treatment of PLE do not influence post-OHT outcomes [22].

Patients with PLE lose albumin, immunoglobulins, and clotting factors resulting in significant fluid overload secondary to low oncotic pressure and an increased infection and thrombosis. The incidence of thrombosis within the Fontan pathway can rapidly become a vicious cycle by increasing

the Fontan pressure further causing rapid clinical deterioration. Two patients were transplanted exclusively for PLE and both had good outcomes. In two others, it was a part of the larger picture of Fontan failure, and both had PA stent with evidence of fresh thrombus in the PA. The presence of thrombus in the recipient PA should specifically be looked at before anastomosing the PA during transplantation. The resolution of PLE occurred by the end of 1 month in the survivors and none of them required albumin transfusion in the postoperative period.

Liver and Fontan

The brunt of elevated CVP of Fontan, first borne by the liver, combined with decreased cardiac output is responsible for Fontan-associated liver disease (FALD). The main risk factor for FALD is the time since surgery. Symptomatic liver disease is unusual, until late, wherein lies the importance of regular liver assessment. This has received increasing attention over the last decade.

The incidence of liver cirrhosis and hepatocellular carcinoma (HCC) increases with the duration of Fontan circulation. The staging of FALD requires a multi-modality approach involving clinical assessment, biochemical parameters, non-invasive fibrosis scores, radiological imaging, elastography, and liver histology. Combined heart-liver transplantation is required in the presence of advanced liver cirrhosis, in the presence of decompensation or localized HCC. Due to the elevation of systemic venous pressure along with the portal venous pressure, porto-systemic venous collaterals are unusual in FALD. This is unlike primary liver cirrhosis wherein the systemic venous pressure is low, and portal venous pressure is high. Bleeding from esophageal varices is rather unusual in FALD [23].

The model for end-stage liver disease (MELD) score is based on bilirubin, creatinine, prothrombin time, need for dialysis in the last week, and sodium ranging from 6 to 40. It is a prospectively validated chronic liver disease scoring system that predicts 3-month survival, in patients with cirrhosis. Since some of the patients are on oral anticoagulants, prothrombin time becomes unreliable and new MELD-XI has been designed excluding INR. The new score has shown a good correlation to the extent of liver fibrosis. The mortality risk varies from 3% for a score of less than 9 to 80% for a score of 40. The importance of the kidney in the survival of patients is emphasized by the fact that 2 of the 5 parameters are directly related to renal function.

Despite growing awareness, the scope and natural history of liver disease in Fontan physiology are unclear and to date, there is no consensus on a reliable noninvasive measure to monitor liver disease. Transient elastography (Fibroscan), an ultrasound-based modality to assess liver fibrosis which correlates with the size of the spleen, and aspartate

transaminase to platelet ratio index (APRI) are two validated noninvasive measures of liver fibrosis in patients with primary liver disease. The presence of liver disease is ubiquitous among patients with Fontan physiology and, at present, liver biopsy is the gold standard to define the severity of the disease. Fibroscan or transient elastography serves to assess the extent of liver fibrosis. It is stratified into 4 stages and is validated for primary liver disease and helps avoid liver biopsy and provides liver stiffness (LS) score. It is falsely high in patients with passive congestion which is its major drawback [24].

MRI elastography is accurate in characterizing liver nodules and has shown a positive correlation with MELD, APRI, Fontan pressure, and histology changes [25].

Histology of the liver initially shows congestion that is manifested by sinusoidal dilatation. There could be zone 3 necrosis of hepatocytes that are close to the hepatic vein. After 5–10 years of Fontan surgery, patients show peri-sinusoidal fibrosis and regenerative nodules and hepatocellular necrosis.

Regenerative nodules appear around the portal tracts secondary to ischemia, which triggers the proliferation of healthy hepatocytes resulting in nodular regenerative hyperplasia. Malignancy in these regenerating nodules is difficult to diagnose. There are, however, some suggestive features: they are hypervascular, show washout, and alpha-fetoprotein is typically elevated. The conclusive diagnosis of HCC, however, requires histological confirmation [25].

Fibrosis at this stage is potentially reversible with heart transplantation. In advanced fibrosis with portal hypertension, hypoalbuminemia, low platelet counts, risk of HCC, and complications of portal hypertension exist. At any stage, a markedly low cardiac output can cause ischemic hepatitis manifested by marked elevation of aspartate aminotransferase (AST), alanine transaminase (ALT), and lactate dehydrogenase (LDH), which is usually reversible, once cardiac output improves [26, 27].

Routine liver biopsies have not been found to be clinically useful. Biopsy is currently recommended when the etiology of liver disease is not clear and in candidates under consideration for heart and liver transplantation [28].

At present, there is no consensus on the indication for combined heart and liver transplant (CHLT). In a retrospective study on heart transplantation for failed Fontan, the presence or absence of radiological evidence of cirrhosis did not influence the outcome. There is evidence in experimental models, where cardiac cirrhosis can reverse with normalization of liver function if the normal cardiac function can be restored [29, 30].

At present, the need for CHLT needs to be decided on a case-to-case basis by a multidisciplinary committee. We have no experience with CHLT, but we have seen regression of advanced fibrosis and regenerative nodules with normalization of hemodynamics and cardiac function post-heart transplantation alone. It seems reasonable in patients with cirrhosis but, normal synthetic function, good liver volume, and no significant portal hypertension and HCC for OHT alone.

While less discussed than FALD, kidney disease is probably under-recognized in patients after Fontan with studies showing reduced glomerular filtration rate, increased risk of glomerular and tubular injury, and chronic kidney disease stage 2 or greater in up to 25% of patients. Preoperative renal failure is known to be a predictor of worse outcomes in all patients post-heart transplant; our own data of close to 320 patients shows that serum creatinine values of > 1.5 mg/dl are one of the most important determinants of not only short-but also long-term outcome [31].

Surgery and postoperative management

Single ventricle patients are heterogeneous in terms of age, anatomic diagnosis, and physiology according to the surgical stage of repair. Our limited experience has taught us some lessons (Table 5). There are numerous factors which increase the risk of transplantation, particularly in those with previous palliations (Table 6).

Table 5 Few observations from our limited experience with a diverse cohort of single ventricle transplantation

- Patients with ventricular dysfunction do better with transplantation than those with failed Fontan physiology
- Unpalliated patients with ventricular dysfunction and pulmonary stenosis form the best subset in terms of postoperative recovery
- Patients with PLE have done well when transplanted with resolution of PLE
- Site of previous Glenn anastomosis should be disconnected and the PA end preferably patch closed as this site is going to be exposed to high pressures by new Right ventricular ejection
- The pulmonary artery should be specifically inspected for any thrombus as this could be contributing to Fontan failure
- Site of pulmonary stenting should be very carefully dealt with, any attempt to extricate the stent is fraught with danger, best managed by cutting across the stent and onlay patching with homologous or bovine pericardium and then anastomosing the donor pulmonary artery to it
- Oversizing of donor heart is difficult due to the small pericardial cavity in the presence of normal ventricular function
- Early Fontan failure with ascites is a bad subset and these patients are possibly better served with taking them down to Glenn and then transplanting rather than from a state of severe systemic venous hypertension
- Patients who require desensitization, who have had previous pulmonary artery interventions, early Fontan (<6 months) failure, and those with ascites are high-risk subset for transplantation

Table 6 Reasons for increased risk for transplantation in those with single ventricle circulation

- Previous surgeries increase the risk of adhesions and bleeding
- Presence of liver and renal dysfunction
- Increased risk of sensitization and increased panel reactive antibodies
- Non-standardized desensitization protocols
- Uncertainties in assessment of pulmonary vascular resistance
- Unfavorable surgical conditions – small pericardial cavity, dilated aorta, thin-walled or stented pulmonary arteries, thin-walled atrial wall
- Low albumin levels delaying healing and leading to tissue edema
- Relative lymphopenia in those with PLE leading to increased risk of infections
- Anatomical variations in systemic and pulmonary veins drainage and in great artery relationship
- Our poor understanding of failed Fontan physiology with normal ventricular function
- Lack of experience in mechanical circulatory support in this population

Careful preoperative planning can help mitigate some of the surgical challenges. Close communication between the donor and recipient team can help reduce cold ischemic time. Extra tissue in the form of an innominate vein, pericardium, and PA bifurcation comes in handy in handling exigencies.

In addition to the challenges of re-entry, the tissue condition in patients with failing Fontan and normal ventricular function can make surgery challenging. The ventricular size is normal resulting in the normal pericardial cavity. There could be extensive pleural adhesions, the aorta is usually dilated, and the PA is thin-walled or stented and may require elaborate reconstruction during the time of transplantation. The atrial tissue is thin and friable—these are contrary to what one encounters in routine heart transplantation for ventricular dysfunction. Oversizing the donor can be dangerous if the pericardial cavity cannot accommodate the heart.

Preparing the bed for donor implantation is the key. Irrespective of the situs, a few constants in any morphology aid the transplant surgeon. The pulmonary veins are posterior midline structure, the aorta and the PA irrespective of their relationship are close to the midline, the pulmonary anastomosis should be kept taut to avoid kinking, and the aortic anastomosis can be a little redundant. The remaining structure is the systemic veins, which need to be baffled to the right to fit into a normal donor.

The recipient cardiectomy has to be done leaving as much native tissue particularly the atrial tissue as possible, which can help in reconstruction. Left superior vena cava (LSVC) is usually managed by using a polytetrafluoroethylene (PTFE) tube to establish a connection to the donor right atrial appendage (Fig. 1). This could be sutured to the recipient LSVC prior to the arrival of the donor heart, or alternatively, the donor heart can be harvested with the innominate vein, which can be anastomosed to the LSVC or the LSVC can be left draining into the coronary sinus and the classic Shumway technique of atrial anastomosis can be adopted. Separately draining hepatic veins can be baffled using the native recipient atrial tissue by constructing a tube, so that they are all routed to the right side, which can then

be anastomosed to the inferior vena caval cuff of the donor (Fig. 2a, b).

Thin-walled left atrial tissue or pulmonary venous chamber in cases of unoperated TAPVC as in one of our cases can be augmented using the recipient atrial tissue or donor pericardium so that the left atrial anastomosis is performed to a cuff of good tissue rather than to thin-walled pulmonary veins (Fig. 3).

Of the children lost, one of them had early Fontan failure (<6 months) and failed salvage of Fontan by stenting the branch pulmonary arteries with ascites and elevated Fontan pressure. The reasons for demise were partly technical where an oversized heart could not be fitted, and the previous multiple surgeries and the recent failed Fontan had resulted in ‘frozen’ mediastinum and pleural cavity with dense adhesions. The stented PA was partly thrombosed and attempted extraction of the stent prevented

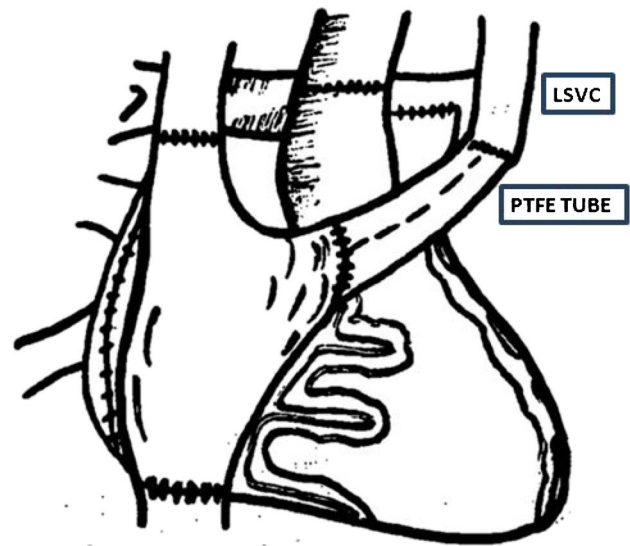


Fig. 1 The interposition PTFE graft connecting the LSVC to right atrial appendage in a patient with common AV canal defect, severe AV valve regurgitation, severe ventricular dysfunction, and bilateral SVC undergoing heart transplant. An appropriately sized PTFE tube matching the size of LSVC was chosen and anastomosed using 6–0 prolene continuous sutures

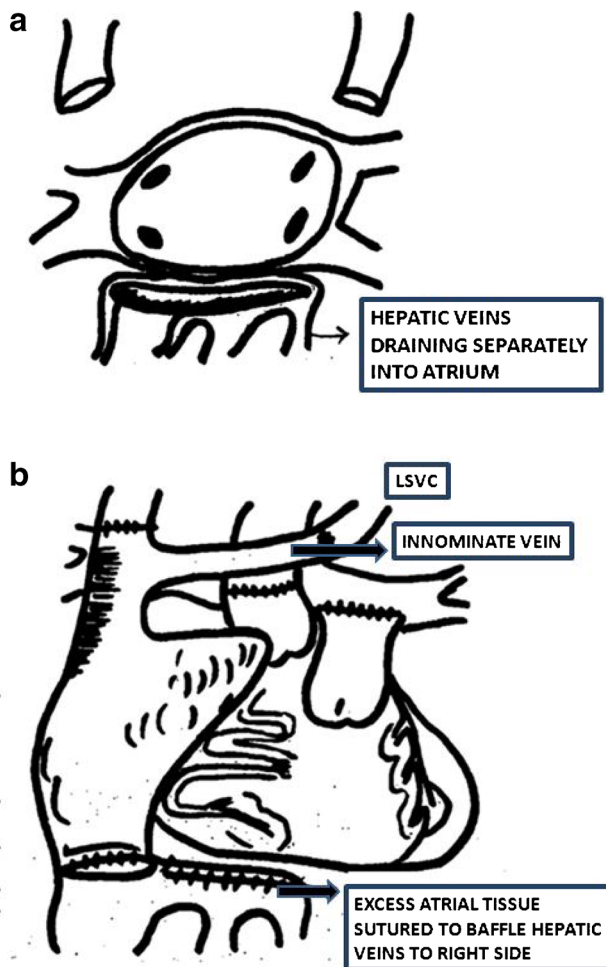


Fig. 2 **a** The hepatic veins draining separately into the right atrium in a patient with heterotaxy syndrome. **b** The methods used to re-route the LSVC and hepatic veins to the right side in a patient undergoing heart transplant for unbalanced AV canal defect, severe ventricular dysfunction, situs ambiguus, hepatic veins opening separately, and bilateral SVC. In this patient, the donor innominate vein was used to connect to the LSVC and the excess recipient atrial tissue was used to baffle the hepatic veins to the right atrium. This re-instates the fact that excess tissue in the recipient can be put to appropriate use by proper anticipation and judgment. The donor harvesting needs to be well planned to suit the recipient's anatomy

hemostatic suturing of the donor PA. The extremely thin-walled atrial tissue had made the left atrial suturing challenging. This case taught us a lot of lessons. Though it is recommended to use an oversized heart in failing Fontan due to vagaries of estimation of PA resistance, it is not always easy to fit an oversized heart in failing Fontan. The pericardial cavity is not big and the heart is not enlarged unlike a patient with dilated cardiomyopathy or with ventricular dysfunction. It is not always possible to cut down on the pleural membrane to accommodate the heart as the lungs could be stuck making that maneuver dangerous and difficult. The stented pulmonary arteries are dangerous to

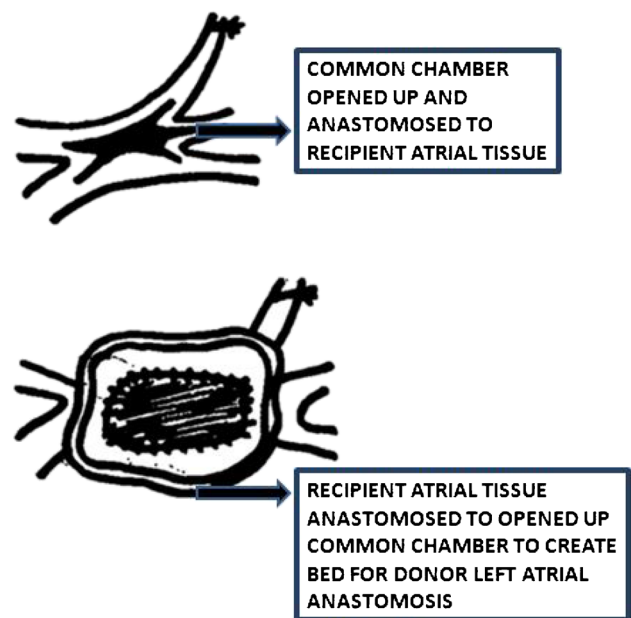


Fig. 3 The technique used in recipient heart transplant in a patient with supra-cardiac total anomalous pulmonary venous return. The common chamber was first opened up and a cuff of recipient atrial tissue was anastomosed to it to create a bed for donor left atrial anastomosis. This was then anastomosed to the donor left atrium

handle and any attempt to remove the stent would leave us with tissue where any form of suturing may not be possible or extremely difficult.

Stented PA poses a special challenge and any attempt at removing the stent can result in catastrophic tearing of already thin-walled PA. They can be managed by reconstructing from hilum to hilum using donor branch pulmonary arteries or using a biological tissue or pericardium as an onlay patch on cut open stent and the anastomosing the donor PA to this patch. Transplanting a complex single ventricle physiology poses special technical and cerebral challenges which most congenital cardiac surgeons can overcome by careful preoperative planning and having extra tissue from the donor for reconstruction.

Postoperative care of these patients can also be challenging. Increased PVR can be unmasked after transplantation, causing RV dysfunction—early consideration may have to be given for ECMO to initially support the RV. These patients are increasingly sensitized and rejection should be carefully watched for. Preoperative desensitization can also increase their chance of infections. PLE could make them nutritionally and immunologically depleted, increasing their risk of invasive infections. The presence of collaterals and pulmonary arteriovenous malformation can lead to post-transplant heart failure and early consideration may have to be given for catheterization and coiling of collaterals [32].

Mechanical circulatory support and ventricular assist device

The experience with ventricular assist device (VAD) in the single ventricle is growing. Patients primarily, those with ventricular dysfunction as their mechanism for failure would benefit from VAD. There may be a role for biventricular assist device (BiVAD) in patients with very high CVP to improve end-organ function, transplant candidacy, and post-transplant outcomes. The survival to transplantation in this group of patients who are on preoperative mechanical assistance has ranged between 25 and 70% [33–35].

We had only one patient with single ventricle physiology who was on pre-transplant central ECMO. Using any form of VAD without oxygenator would require the separation of the systemic and pulmonary circulation and complicate surgical management. We opted for central ECMO with atrial septostomy to simplify management considerations. The young girl had severe ventricular dysfunction with markedly elevated CVP, with single ventricle physiology with the previous shunt with end-organ damage and impending cardiac arrest. She was placed on central ECMO, with clipping of shunt, with atrial and aortic cannulation with the cannula brought out through the chest wall with sternum closed. She was extubated, mobilized, and nutritionally rehabilitated. Her end-organ functions improved and she underwent successful heart transplantation after 2 weeks on ECMO with an uneventful postoperative period. At 3 years' follow-up, she is doing well. Practical considerations and financial implications would mean that ECMO may be the best form mechanical assistance that could be provided in our setup to single ventricle population. These patients should be prioritized to receive donor organ after the resolution of end-organ dysfunction to optimize their long-term outcome, as complications on ECMO increase exponentially after 7–10 days. We have not used ECMO postoperatively in this group of patients.

Financial considerations

This poses a unique and formidable challenge to the treating team, the patient family, and the hospital in the subcontinent

Table 7 Knowledge gaps in understanding palliated single ventricle circulation and heart transplantation for failed single-ventricle palliation

- The understanding of lymphatic physiology in the setting of chronic venous hypertension
- The effect of chronic venous hypertension on the functioning of the liver and kidneys
- Estimating pulmonary vascular resistance in the presence of non-pulsatile circulation and presence of decompressing collaterals
- The hepatic factor and the reason for pulmonary arteriovenous malformation
- The role of panel reactive antibodies, sensitization, and the need and protocol for desensitization
- The role of lymphatic procedures, medications, non transplant palliative procedures like fenestration and stenting for Protein losing enteropathy and plastic bronchitis and the timing and indication of transplantation in the presence of normal ventricular function
- Predicting the behavior of donor right ventricle in the presence of elevated pulmonary vascular resistance

where government funding is essentially almost non-existent and the cost has to be borne by the patient family.

The support of a non-governmental organization (Aishwarya Trust), state government (CMCHIS – Chief Minister Comprehensive health insurance scheme), and considerate hospital management (Fortis Malar and MGM healthcare) and the quality of life of treated patients motivate us to continue our work despite all the odds.

Future

Fontan and other single ventricle palliation procedures have, no doubt, improved the quality of life, but are we justified in taking everyone down this pathway? While we have pushed the boundaries of performing Fontan, we need to question if we have improved their quality of life. Increasing our focus on understanding the lymphatics in single-ventricle patients would help us screen ideal candidates for Fontan palliation [36, 37]. There are numerous knowledge gaps that need to be addressed (Table 7).

The best results of heart transplantation in single ventricle physiology patients are those in whom the pulmonary circulation is protected and there is ventricular dysfunction with no previous palliation, or only stage I or stage II palliation with systemic to PA shunt or Glenn. We need to identify patients who are at high risk for Fontan procedure; the use of hemodynamic modeling and lymphatic screening using MRI may help to perform tailored Fontan for the individual anatomy and select outpatients who are at high risk of lymphatic complications post Fontan. The use of mechanical cavopulmonary assist may also have a role to play. Generation of 10–15 mm Hg additional pressure to reverse the Fontan paradox, a long-term implantable durable cavopulmonary assist device, based on Von Karman viscous flow principle [37] may also help address the problem of limited donors and to improve the end-organ function while the patient is awaiting transplantation [38]. Lymphatic imaging and lymphatic procedures would have an increasing role to play in alleviating symptoms and improving outcomes [39, 40].

Conclusion

A better understanding of the indication and selection of patients coupled with a better understanding of immunology would help improve the outcomes in this extremely heterogeneous and challenging cohort of patients and would ultimately help in better utilization of limited donor organ resources, improving outcomes and quality of life. There is an urgent need to evolve a national database to understand which subset of patients are not good candidates for Fontan completion. High-risk single ventricle palliation in the form of Glenn or Fontan especially in the presence of the ventricular dysfunction provides much inferior palliation and quality of life than can be provided by transplantation. The unpalpated subset of patients with ventricular dysfunction and reduced pulmonary flow is the best subset for heart transplantation with excellent short- and long-term outcomes.

Limitations of study

The main limitations of the study were the small sample size and the heterogeneous nature of the study subset. Also, the retrospective nature of the study had a few issues with data collection. However, the data collection was done as completely, meticulously, and genuinely as possible.

Funding None.

Declarations

Ethics approval and informed consent This study was reviewed and discussed by the Institutional Ethics Committee and permission was granted to utilize the data for publication. Informed consent of patients was obtained for the study.

Statement of human and animal rights All procedures performed were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Conflict of interest The authors declare no competing interests.

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