Lessons Learned From 119 Consecutive Cardiac Transplants for Pediatric and Congenital Heart Disease


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Lessons Learned From 119 Consecutive Cardiac Transplants for Pediatric and Congenital Heart Disease

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Background. This manuscript reviews all patients who underwent orthotopic heart transplantations (OHT) at our program (116 patients underwent 119 OHT) to describe their diagnostic characteristics and to assess risk factors for mortality.

Methods. Median age at OHT was 179 days (mean, 1,446.6 ± 188.9 days [4.0 ± 0.5 years]; range, 5 days to 7,125 days [19.5 years]; 15 neonates, 68 infants). Median weight at OHT was 5.5 kg (mean, 17.2 ± 2.1 kg; range, 2.2 to 113 kg). Diagnoses were cardiomyopathy (n = 37), primary transplantation for hypoplastic left heart syndrome (HLHS) or HLHS-related malformation (n = 29), transplantation after prior cardiac surgery for HLHS or HLHS-related malformation (n = 9), non-HLHS congenital heart disease (n = 39), and retransplant (n = 5).

Results. Overall Kaplan-Meier 5-year survival was 72.7%. Operative mortality was 12.6% (15 patients). Late mortality was 13.4% (16 patients). Eighty-five patients survived, with a mean follow-up of 5.76 ± 0.48 years (median, 5.1 years; range, 0.12 to 14.0 years). Total follow-up was 507.0 years. No survival difference was seen among the five diagnostic subgroups (p = 0.20). Univariate association between risk factors and survival was assessed for the following variables: age (p = 0.91), weight (p = 0.86), sex (p = 0.47), race (p = 0.40), insurance classification (p = 0.42), high PRA (p = 0.20), pretransplant mechanical circulatory support (p < 0.001), posttransplant mechanical circulatory support (p < 0.001), redo sternotomy (p = 0.07), heterotaxy (p = 0.02), cardiopulmonary bypass time (p = 0.01), and donor heart cross-clamp time (p = 0.02).

Conclusions. Excellent results are expected for children undergoing OHT regardless of diagnostic classification. Pretransplant mechanical circulatory support, posttransplant mechanical circulatory support, cardiopulmonary bypass time, donor heart cross-clamp time, and heterotaxy are risk factors for decreased survival.


At All Children’s Hospital, we performed our first heart transplant on June 19, 1995. In September of 2009, we comprehensively reviewed all patients who underwent cardiac transplantation at our program, a cohort of 116 patients who underwent 119 orthotopic heart transplantations (OHT) as treatment for pediatric and congenital heart disease. As our program gained experience with OHT, we began offering OHT to patients with diagnoses and factors thought to be associated with higher risk, including patients with elevated panel reactive antibody (PRA), patients with hypoplastic left heart syndrome (HLHS) who have failed previous surgical intervention, and patients bridged to OHT with mechanical circulatory support devices including extracorporeal membrane oxygenation and ventricular assist devices.

In 2004, we published our initial experience with OHT in patients with elevated PRA (≥10%) and reported that although OHT can offer children with end-stage heart failure and elevated PRA their only chance of survival, overall survival after OHT seems to be worse for those patients with an elevated PRA compared with those without elevated PRA [1]. We have since modified our immunosuppression protocol for patients with elevated PRA in an effort to improve their prognosis. In 2006, we published our initial experience with OHT as treatment for failing staged palliation in patients with HLHS and reported that although OHT can offer children with...
Table 1. Univariable Association Between Five Diagnostic Subgroups and Survival

<table>
<thead>
<tr>
<th>Patient Group</th>
<th>Number of OHTs</th>
<th>Operative Mortality Number % (95% CI)</th>
<th>Late Mortality Number %</th>
<th>Estimated 5-Year Survival % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiomyopathy</td>
<td>37</td>
<td>3</td>
<td>8.1% (1.7%, 21.9%)</td>
<td>4</td>
</tr>
<tr>
<td>Primary transplantation for HLHS or HLHS-related malformation</td>
<td>29</td>
<td>2</td>
<td>6.9% (0.8%, 22.8%)</td>
<td>5</td>
</tr>
<tr>
<td>Transplantation status post prior cardiac surgery for HLHS or HLHS-related malformation</td>
<td>9</td>
<td>3</td>
<td>33.3% (7.5%, 70.1%)</td>
<td>2</td>
</tr>
<tr>
<td>Non-HLHS congenital heart disease</td>
<td>39</td>
<td>6</td>
<td>15.4% (5.9%, 30.5%)</td>
<td>5</td>
</tr>
<tr>
<td>Retransplant</td>
<td>5</td>
<td>1</td>
<td>20.0% (0.5%, 71.6%)</td>
<td>0</td>
</tr>
</tbody>
</table>

CI = confidence interval; HLHS = hypoplastic left heart syndrome; OHT = orthotopic heart transplant; * = Unable to estimate due to small sample size.

failing staged palliation of HLHS their only chance of survival, OHT carries a high risk in this subgroup, especially in the setting of elevated PRA [2]. The purpose of this manuscript is to describe the diagnostic characteristics of all patients who underwent OHT at our program, and to assess risk factors for mortality.

Material and Methods

Patient Characteristics

One hundred nineteen consecutive OHTs have been performed in 116 patients. Patients were in the following three age categories at the time of OHT: neonates (≤30 days at OHT; n = 15), infants excluding neonates, (≥30 days and <1 year; n = 53), and children (≥1 year; n = 51). All patients in this series were younger than 17 years of age at the time of OHT except for 1 patient who was 19.5 years at OHT with the diagnosis of pulmonary atresia and intact ventricular septum status after biventricular repair with severe biventricular dysfunction. Mean age at OHT was 1,446.6 ± 188.9 days (4.0 ± 0.5 years). Median age at OHT was 179 days, with a range of 5 days to 7,125 days, or 19.5 years. Mean weight at OHT was 17.2 ± 2.1 kg. Median weight at OHT was 5.5 kg, with a range of 2.2 to 113 kg.

Table 1 stratifies the 119 OHTs into five diagnostic subgroups. The five retransplants included 3 patients who underwent their initial OHT at our program and 2 patients who underwent their initial OHT elsewhere.

In the second half of the 1990s, The Congenital Heart Institute of Florida (CHIF) used both primary cardiac transplantation and staged palliation as treatment for HLHS [3]. We have now evolved our program such that the overwhelming majority of our patients with HLHS and HLHS-related malformations are now treated with staged palliation via the “Norwood” approach; we now only use primary cardiac transplantation for HLHS selectively for very specific indications. We now selectively offer transplantation for HLHS in the setting of significant ventricular dysfunction, severe atroventricular or ventriculoarterial valvar regurgitation, severe tricuspid to coronary artery fistulas with ventriculo-dependent coronary circulation [4], strong family preference, and for patients experiencing failure at any point in the process of staged palliation. Between 1995 and 2002, inclusive, 21 patients underwent primary cardiac transplantation as treatment for HLHS. Between 2003 and 2009, inclusive, only 8 patients underwent primary cardiac transplantation as treatment for HLHS. Meanwhile, between 1995 and 2002, inclusive, 105 patients underwent the Norwood (Stage 1) procedure at CHIF, and between 2003 and 2009, inclusive, 136 patients underwent the Norwood (Stage 1) procedure at CHIF.

Several OHTs were in one or more potentially high-risk subgroups: (1) high PRA (>10%; n = 15); (2) patients with HLHS who have failed previous surgical intervention (n = 9); (3) pretransplant mechanical circulatory support (n = 16); (4) posttransplant mechanical circulatory support (n = 6); (5) retransplantation (n = 5); and (6) intentional ABO-incompatible OHT (n = 1). Of the 16 OHTs with pretransplant mechanical circulatory support, 1 had an intraaortic balloon pump, 6 had ventricular assist devices (4 Abiomed and 2 Berlin Heart), and 11 had extracorporeal membrane oxygenation (2 patients with extracorporeal membrane oxygenation were transitioned to the Berlin Heart). Several OHTs belonged to more than one high-risk group; for example, 4 of the 9 patients undergoing transplantation after prior cardiac surgery for HLHS or HLHS-related malformation also had high PRA.

Operative Technique

Operative technique involves bicaval cannulation and anastomoses with continuous low-flow bypass and either short periods of circulatory arrest or continuous antegrade cerebral perfusion for aortic arch reconstruction in HLHS. The bicaval implantation technique is used with a superior vena cava reconstruction with a spatulated sliding cavopulmonary connection. After bridging to transplantation, the heart is rewarmed at a perfusion temperature of 32°C. Grade cerebral perfusion for aortic arch reconstruction in HLHS. The bicaval implantation technique is used with a superior vena cava reconstruction with a spatulated sliding cavopulmonary connection. After bridging to transplantation, the heart is rewarmed at a perfusion temperature of 32°C. Mechanical circulatory support is used when necessary as a bridge to transplantation and to support marginal donor hearts.

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Protocol for Immunosuppression and Surveillance

Before 2005, PRA was determined using cytotoxic PRA assay and dithiothreitol-treated assay to factor out immunoglobulin M and measure the highest immunoglobulin G. We now assess PRA by flow cytometry.

For patients without high PRA, our current protocol for immunosuppression includes the following regimens for induction and maintenance: for induction, standard Solu-Medrol pulse is administered at a dose of 7.5 mg/kg per dose every 12 hours for eight doses. Also, Thymoglobulin is administered at a dose of 1 mg/kg for 5 days, except for patients with suspected infection or delayed sternal closure who receive Daclizumab 1 mg/kg every 14 days for five doses instead. For maintenance, Tacrolimus and mycophenolate mofetil (MMF-CellCept; Roche Laboratories, Nutley, NJ) are used. Cyclosporin is used for maintenance in patients who do not tolerate Tacrolimus, and Sirolimus or Azathioprine is used for maintenance in patients who do not tolerate MMF). Also, oral prednisolone or prednisone is given at a dose of 1 mg/kg per dose twice daily for 2 weeks with weaning during the first 3 months.

For patients with high PRA, our current protocol for immunosuppression includes the following regimens for preinduction, induction, and maintenance: preinduction, while on the waiting list, from the time of listing until the time of transplantation: (1) potential recipients are given monthly pulse cyclophosphamide (Cytoxan) at a dose of 1000 mg/m² in patients of at least 0.5 m² body surface area or 33 mg/kg in patients of less than 0.5 m² body surface area; (2) potential recipients are given weekly intravenous immunoglobulin G (IVIG); (3) potential recipients undergo weekly plasmapheresis (if the patient is of suitable size). Preoperative and postoperative (up to 5 days) exchange transfusions (infants) or plasmapheresis (children) is also used. Then, patients with high PRA receive the same induction and maintenance as those without high PRA. We reserve the administration of Rituximab for patients with high PRA who also have high titers of individual anti-HLA preformed antibodies before transplant, or patients who have rapidly rising donor-specific antibody titers after transplant.

For patients without high PRA, our protocol for immunosuppression before 2006 was as follows: induction immunosuppressive therapy included pulse steroids for 4 days, gamma globulin, and polyclonal rabbit antithymocyte globulin. Initial immunosuppression was a double-dose regimen: a calcineurin inhibitor (cyclosporin A or tacrolimus [Prograf], usually cyclosporin A) and an antiproliferative agent (either azathioprine [Imuran] or MMF to target levels of 2 to 4).

For patients with high PRA, our protocol for immunosuppression before 2006 was as follows: preoperative intravenous immunoglobulin G was given weekly or preoperative cyclophosphamide (Cytoxan) or MMF was given daily from the time of listing until the time of transplantation. Preoperative and postoperative (up to 5 days) exchange transfusions (infants) or plasmapheresis (children) was used. Also, cyclophosphamide (Cytoxan; 1 mg/kg per day) was the initial antiproliferative agent with conversion to MMF when oral intake was established.

Rejection surveillance is conducted by echocardiography, echocardiographically guided endomyocardial biopsy, as previously described [5–9], and protocol-timed biopsies. Echocardiographic surveillance of systolic and diastolic function predicts biopsy abnormalities and decreases the number of cardiac catheterizations. Biopsy is performed when the echocardiogram is suggestive of rejection. Significant rejection is defined as intensification of immunosuppression associated with an abnormal biopsy (International Society of Heart and Lung Transplantation grade 3 or higher using the old classification, or Grade 2R or higher using the new classification) or new-onset hemodynamic abnormalities confirmed by echocardiography. Posttransplant retrospective crossmatching was performed on all patients. No prospective crossmatching was performed in our program before 2005. However, since January 2005, we do perform prospective virtual crossmatch on all highly-sensitized patients prior to accepting an organ.

Statistics and Database

Operative mortality was defined as death within the same hospitalization as OHT or after discharge but within 30 days of OHT. Deaths that did not meet the definition of operative mortality were described as “late mortality.” The percentage frequency of operative mortality was calculated overall and within subgroups using exact 95% binomial confidence intervals. The Kaplan-Meier method was used to estimate post-transplant survival probabilities as a function of time since OHT. Pointwise 95% confidence intervals were obtained using the Greenwood variance estimator. Log-rank tests were used to compare survival between subgroups. The unadjusted association between each candidate risk factor and mortality was assessed in a series of univariable Cox proportional hazards models. Each model produced a hazard ratio comparing patients with versus without the risk factor of interest, as well as a 95% confidence interval and a score-based (log-rank) p-value. The unit of analysis for these Cox model analyses was a patient. Other analyses were either based on patients (N = 116) or OHTs (N = 119). Analyses of OHTs did not account for within-patient correlation resulting from 3 patients who each contributed 2 OHT operations. Results were virtually identical when only the first OHT per patient was analyzed. No formal adjustment for multiple comparisons was made. Given the small number of patients and deaths, multivariable analyses were not considered stable and were not performed. All analyses were performed using S-Plus version 6.1 (Insightful Corp, Seattle, WA). A p value < 0.05 was considered to be significant.

A registry and database (a component of the CardioAccess International Clinical Outcomes Database: Comprehensive Cardiovascular and Thoracic Module, CardioAccess Inc, St. Petersburg, FL, and Fort Lauderdale, FL: http://www.cardioaccess.com) has been prospectively maintained on all patients and has been used for data.
collection and analysis. Institutional review board approval and waiver of the need for consent have been obtained (ACH IRB protocol number 03-0513).

Results

Overall Kaplan-Meier 5-year survival was 72.7%. Operative mortality was 12.6% (15 patients) [10]. Late mortality was 13.4% (16 patients). Eighty-five patients are alive with a mean follow-up of 5.76 ± 0.48 years. Median follow-up was 5.1 years (range, 0.12 to 14.0 years). Total follow-up was 507.0 years.

Table 1 reports operative mortality, late mortality, and estimated 5-year survival for five diagnostic subgroups. No difference in survival was seen among the five diagnostic subgroups (p = 0.20). Table 2 reports operative mortality, late mortality, and estimated 5-year survival for additional cohorts. Our 1 patient who underwent intentional ABO-incompatible OHT died on postoperative day 325 after aspiration at home.

Univariate analysis of the association of the following factors with mortality was performed: age, neonate, infant, weight, sex, race, insurance classification, cardiomyopathy, high PRA, pretransplant mechanical circulatory support, posttransplant mechanical circulatory support, redo sternotomy, heterotaxy, cardiopulmonary bypass time, and donor heart cross-clamp time (Table 3). The following factors were found to be significantly associated with mortality: pretransplant mechanical circulatory support (p < 0.001), posttransplant mechanical circulatory support (p < 0.001), cardiopulmonary bypass time (p = 0.01), donor heart cross-clamp time (p = 0.02), and heterotaxy (p = 0.02). Given the small number of patients and events, multivariable analyses of time-to-event data were considered unstable and were not performed.

Kaplan-Meier Survival Analyses

Figure 1 shows overall survival of all 116 patients with a Kaplan-Meier analysis of patient survival from the time of first OHT at The Congenital Heart Institute of Florida (CHIF) and All Children’s Hospital.

Figure 2 documents the Kaplan-Meier analysis of patient survival by stratified diagnostic category for the most common diagnoses: cardiomyopathy (n = 37), primary transplantation for HLHS or HLHS-related malformation (n = 29), and non-HLHS congenital heart disease (n = 39). This figure demonstrates that survival is not statistically different in these three diagnostic groups (p = 0.54).

Figure 3 documents the Kaplan-Meier analysis of patient survival by diagnostic category for patients with the diagnosis of HLHS or HLHS-related malformation (n = 38), and compares primary transplantation for HLHS or HLHS-related malformation (n = 29) with transplantation after prior cardiac surgery for HLHS or HLHS-related malformation (n = 9). This figure documents that

Table 3. Univariable Association Between Patient Factors and Survival

<table>
<thead>
<tr>
<th>Factor</th>
<th>Hazard Ratio (95% CI)</th>
<th>Log-Rank p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (per year)</td>
<td>1.00 (0.94, 1.07)</td>
<td>0.91</td>
</tr>
<tr>
<td>Neonate (vs child)</td>
<td>0.51 (0.11, 2.31)</td>
<td>0.34</td>
</tr>
<tr>
<td>Infant (vs child)</td>
<td>1.42 (0.67, 3.03)</td>
<td>0.35</td>
</tr>
<tr>
<td>Weight</td>
<td>1.00 (0.98, 1.01)</td>
<td>0.86</td>
</tr>
<tr>
<td>Sex (female)</td>
<td>0.77 (0.38, 1.57)</td>
<td>0.47</td>
</tr>
<tr>
<td>Race (non-white race)</td>
<td>1.38 (0.65, 2.95)</td>
<td>0.40</td>
</tr>
<tr>
<td>Insurance classification</td>
<td>1.39 (0.62, 3.12)</td>
<td>0.42</td>
</tr>
<tr>
<td>Cardiomyopathy</td>
<td>0.66 (0.28, 1.54)</td>
<td>0.33</td>
</tr>
<tr>
<td>High PRA</td>
<td>1.86 (0.71, 4.99)</td>
<td>0.20</td>
</tr>
<tr>
<td>Pretransplant mechanical</td>
<td>3.82 (1.73, 8.44)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Posttransplant mechanical</td>
<td>5.23 (1.81, 15.11)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Redo sternotomy</td>
<td>1.92 (0.95, 3.90)</td>
<td>0.07</td>
</tr>
<tr>
<td>Heterotaxy</td>
<td>3.72 (1.12, 12.37)</td>
<td>0.02</td>
</tr>
<tr>
<td>Cardiopulmonary bypass time</td>
<td>1.40 (1.10, 1.78)</td>
<td>0.01</td>
</tr>
<tr>
<td>Donor heart cross-clamp time</td>
<td>1.22 (1.04, 1.43)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

CI = confidence interval; PRA = panel reactive antibody.
survival after transplantation after prior cardiac surgery for HLHS or HLHS-related malformation appears to be worse than survival after primary transplantation for HLHS or HLHS-related malformation ($p = 0.05$).

Figure 4 documents the Kaplan-Meier analysis of patient survival for all patients comparing patients with high PRA ($n = 13$) with patients without high PRA ($n = 103$) and demonstrates no significant increase in risk for patients with high PRA ($p = 0.20$). (Patients who underwent retransplantation are only shown in this figure for their initial transplant. Two patients with high PRA at the time of retransplantation are still alive today.)

Figure 5 documents the Kaplan-Meier analysis of patient survival for all patients comparing survival in patients undergoing primary transplantation ($n = 114$) with...
the 7 patients who had failing staged palliation, 3 had undergone a Norwood Stage 1 operation and a Glenn superior cavopulmonary anastomosis, and 2 had undergone a Norwood Stage 1 operation, a Glenn superior cavopulmonary anastomosis, and a completion Fontan operation. The group undergoing primary transplantation was younger (p = 0.007), weighed less (p = 0.003), and waited longer for an appropriate donor heart (p = 0.021) compared with those requiring rescue transplantation. No significant difference existed between the groups with regard to donor heart ischemic time or posttransplant length of hospital stay. Thirty-day survival (p = 0.156) and overall survival (p = 0.053) were better in those having primary transplantation, although these differences were not statistically significant when a probability value of less than 0.05 is considered to be significant. In those having primary transplantation, no patients had elevated PRA of greater than 10%. Half of the 8 requiring rescue transplantation had PRA of greater than 10%, and this subgroup did especially poorly. Our current analysis again reveals that survival after transplantation after prior cardiac surgery for HLHS or HLHS-related malformation appears to be worse than survival after primary transplantation for HLHS or HLHS-related malformation, although the statistical significance is marginal (p = 0.05).

In 2004, we published that cardiac transplantation can offer children with failing staged palliation of HLHS their only chance of survival; however, transplantation carries a high risk in this subgroup, especially in the setting of elevated PRA. In this 2006 analysis of the 31 patients with HLHS, 23 underwent primary transplantation, and 8 underwent rescue transplantation from failing staged palliation in 7, or attempted biventricular repair in 1. Of the 7 patients who had failing staged palliation, 3 had undergone only the Norwood Stage 1 operation, 2 had undergone a Norwood Stage 1 operation and a Glenn superior cavopulmonary anastomosis, and 2 had undergone a Norwood Stage 1 operation, a Glenn superior cavopulmonary anastomosis, and a completion Fontan operation. The group undergoing primary transplantation was younger (p = 0.007), weighed less (p = 0.003), and waited longer for an appropriate donor heart (p = 0.021) compared with those requiring rescue transplantation. No significant difference existed between the groups with regard to donor heart ischemic time or posttransplant length of hospital stay. Thirty-day survival (p = 0.156) and overall survival (p = 0.053) were better in those having primary transplantation, although these differences were not statistically significant when a probability value of less than 0.05 is considered to be significant. In those having primary transplantation, no patients had elevated PRA of greater than 10%. Half of the 8 requiring rescue transplantation had PRA of greater than 10%, and this subgroup did especially poorly. Our current analysis again reveals that survival after transplantation after prior cardiac surgery for HLHS or HLHS-related malformation appears to be somewhat worse than survival after primary transplantation for HLHS or HLHS-related malformation (p = 0.05; Fig 3).

In 2004, Kanter and colleagues [11] reported that “cardiac retransplantation can be performed in children with results comparable with those for primary transplantation despite increased clinical acuity. These early results suggest that cardiac retransplantation in children is a reasonable therapeutic option.” In 2005, a subsequent analysis of data from the United Network for Organ Sharing [12] concluded that “survival after cardiac retransplantation in children is inferior to that after primary transplantation. Although results are acceptable, the impact of retransplantation on the availability of donor hearts requires further consideration.” Our current study found no increase in risk for those undergoing retransplantation (p = 0.87; Fig 5), although only 5 of our transplants were retransplants.

Comment

Excellent results can be expected for children undergoing cardiac transplantation regardless of their diagnostic classification. Pretransplant mechanical circulatory support, posttransplant mechanical circulatory support, cardiopulmonary bypass time, donor heart cross-clamp time, and heterotaxy are risk factors for decreased survival. Of note, elevated PRA no longer appears to be a significant risk factor, and retransplantation is not a risk factor. Survival after transplantation after prior cardiac surgery for HLHS or HLHS-related malformation appears to be worse than survival after primary transplantation for HLHS or HLHS-related malformation, although the statistical significance is marginal (p = 0.05).

In 2004, we published that cardiac transplantation can offer children with end-stage heart failure and elevated PRA their only chance of survival; however, these patients remain high risk despite aggressive immunosuppression. In this report from 2004, 30-day mortality for patients with PRA was 25% and for those without high PRA was 7.9% (p = 0.178). Overall mortality for patients with high PRA was 50% and for those without high PRA was 15.4% (p = 0.043).

Since 2004, we have modified our protocol for immunosuppression in patients with elevated PRA by administering monthly pulse cyclophosphamide (with less cumulative dose and side effects), and by using rituximab for the subgroup with high individual titers and rising donor-specific antibody titers after transplant. In our report from 2004, 30-day mortality for transplantation with high PRA was 25% and overall mortality for transplantation with high PRA was 50%. After modification of our protocols, 30-day mortality for transplantation with high PRA is now 13.3%, and overall mortality for transplantation with PRA is 33%. This current study shows that elevated PRA may no longer be a significant risk factor for survival with modern immunosuppressive protocols (Fig 4).
have access to better support devices than ever. Heart failure remains a leading cause of death worldwide. Current therapies only delay progression of the cardiac disease or replace the diseased heart with cardiac transplantation [13]. Future research in the areas of pediatric mechanical circulatory support devices and opportunities for cardiac regeneration should lead to improved outcomes for children with cardiac failure. Stem cells represent a recently discovered novel approach to the treatment of cardiac failure that may facilitate the replacement of diseased cardiac tissue and subsequently lead to improved cardiac function and cardiac regeneration [13]. For now, cardiac transplantation remains the mainstay of treatment for end-stage cardiac failure, and outcomes continue to improve, even in high-risk patients.

Excellent results can be expected for children undergoing cardiac transplantation regardless of their diagnostic classification. This consecutive series of 119 pediatric cardiac transplant operations identifies the following risk factors for decreased survival: (1) pretransplant mechanical circulatory support, (2) posttransplant mechanical circulatory support, (3) cardiopulmonary bypass time, (4) donor heart cross-clamp time, and (5) heterotaxy. Of note, elevated PRA no longer appears to be a significant risk factor, and retransplantation is not a risk factor. Survival after transplantation after prior cardiac surgery for HLHS or HLHS-related malformation appears to be worse than survival after primary transplantation for HLHS or HLHS-related malformation.

References

DISCUSSION

DR KRISTINE GULESERIAN (Dallas, TX): Thank you, Dr Jacobs, for a great presentation and for sending the manuscript and the slides in advance. I have to say I nearly had a seizure when looking at slide number 11.

Now, when we look back at the beginnings of pediatric heart transplantation, and, for that matter, when we look back at adult cardiac transplantation, we are reminded of the pioneering efforts of such giants as Dr Adrian Kantrowitz, who performed the very first human pediatric heart transplantation in the United States back in December of 1967 just 3 days after Dr Christiana Barnaard’s landmark operation in Capetown, South Africa, on December 3, 1967, before many of us in this room were even born, and then later Dr Leonard Bailey, who performed the very first baboon to human heart transplant in a 12-day-old infant with hypoplastic left heart syndrome named Stephanie Fae Beauchlair, better known to us as Baby Fae, the 25th anniversary of which we just celebrated last week. I think it is important to realize that these historic efforts have set the stage for pediatric heart transplantation and have enabled us to be able to be here today to discuss results and outcomes of infants and children who have undergone cardiac transplantation.

While the numbers of the potential cardiac transplant recipients continues to steadily increase due to improvements in our medical therapy and surgical intervention as well as the numbers of patients with congenital heart disease who are becoming young adults and older adults, the same does not hold true for the numbers of donors out there, and that translates into significant wait list mortality, reported in the literature anywhere from 15% to 30%, even in the most contemporary series. And we certainly know that the use of pediatric donor hearts declined by one or more than one institution based on the 830 or donor quality code does not seem to adversely impact graft and/or patient survival as presented in the data by Dr Len Bailey and his group at Loma Linda at our 2009 STS (The Society of Thoracic Surgeons) meeting last January and as recently published in the Annals of Thoracic Surgery in June. So this leads to the identification of recipient risk factors, whether they are preoperative, intraoperative, or postoperative time periods, as potential areas of investigation for improvement when we are
looking at survival. Interestingly in their series, longer donor ischemic time did not impact graft or patient survival.

Now, Dr Jacobs has just described his single-center experience with these 119 transplants, and my first question, aside from the obvious as to whether you really think you are a top contender for the Tiki Award, would be, how generalizable do you think that your individual center’s results can be to other centers when we know all too well that many pediatric cardiac surgical series are confounded by a low N and that comparison of results between individual centers may be further confounded by differences in recipient selection, wait list mortality, and pulmonary venous drainage. Add to that the inclusion of the highly sensitized or even the completely sensitized patient and the need for preoperative mechanical ventilatory support that has come out as a risk factor in other series, as well as the on-pump support, which you so nicely outlined, as well as the center-specific differences in immunosuppressive and surveillance strategies, how do we compare results and outcomes?

And question two, did you look at wait list mortality, and, if so, did that make an impact on your results? In other words, were highly sensitized patients or other high-risk patients just never transplanted and thus never considered in the analysis?

DR JACOBS: Thank you, Kris. I am aware of the important research that you do as part of the Pediatric Heart Transplant Study Group (PHTSG), so I am very pleased that you are the person who is discussing this paper.

I will begin my answer by briefly commenting on the beginning of your discussion. I agree that we have a lot to be thankful for from the founders of our profession who started pediatric heart transplantation. A few years ago at our hospital, we had Len Bailey and his wife Nancy present a wonderful lecture about their experience with Baby Fae. At All Children’s Hospital, we have a lecture named after the founder of our cardiac surgical program, George Daicoff. George is one of the early members of the Southern Thoracic Surgical Association. In fact, George won the President’s Award at the Southern in 1970 and he won the Osler Abbott Award at the Southern in 1996. Anyway, in 2003, Len and Nancy Bailey visited our hospital and gave a great talk for the Daicoff lecture. They talked about the entire Baby Fae experience, including the sacrifices made by the Bailey family and the family of Baby Fae. It is certain that we are where we are now in the field of pediatric cardiac transplantation because of the tremendous efforts and sacrifices made by those that developed the field, including Len and Nancy Bailey. Kris, I agree with you that all of us should be thankful for this.

Now, your question about wait list mortality is very important. When one analyzes the outcomes of subsets of patients who may be candidates for cardiac transplantation or who are treated with transplantation, one must factor in those that die on the wait list. In our own program, we have not denied transplantation, or listing for transplantation, to any patients because of high PRA (panel reactive antibody). We have been very aggressive in transplanting children with high PRA, and we were one of the first centers to do that in children. In fact, in 2003, we presented our early experience with pediatric cardiac transplantation in children with high panel reactive antibody at the annual meeting of the Southern Thoracic Surgical Association.

Finally, I think that your comment about the generalizability of a single institutional series like this series raises an extremely important question. In some areas, the findings we had with our 119 heart transplants are identical to what is reported in the literature, while in other areas, the findings are a bit different. Regardless, these findings document what we found in our series, that is, what happened in Saint Petersburg, Florida. I believe that the best way to study these questions is with multi-institutional registries. It was mentioned in the previous presentation that multi-institutional registries have some limitations when they are administrative registries and not clinical registries. I think the ultimate solution is through strategies to link the STS Database to other databases like the databases of UNOS (United Network for Organ Sharing) or the Pediatric Heart Transplant Study Group (PHTSG), so that analyses can capitalize on the unique advantages of the different data sets. I do know that some early discussions have taken place regarding the possibility of linking the STS Congenital Heart Surgery Database to a variety of databases, including the database of the Pediatric Heart Transplant Study Group. I think that strategies to link together several multi-institutional registries represent probably the best way to answer some of these questions.

Kris, thanks for your excellent questions and for your leadership in the Pediatric Heart Transplant Study Group.

DR ROBERT JAQUISS (Little Rock, AR): I just wanted to say, Jeff, that I think that not all mechanical support in children is the same.

DR JACOBS: Agreed.

DR JAQUISS: Betsy Bloom has shown, at least in larger children, that LVADs (left ventricular assist devices) provide a survival that is equivalent to status 1As that aren’t supported with mechanical support. That is not true with ECMO (extracorporeal membrane oxygenation). And in our own series with the introduction of the Berlin Heart, we have seen our wait list mortality, which historically has been about 18%, go to under 5%, and I think you will see the same thing.

DR JACOBS: Jake, I agree with that completely. With a 7-minute presentation, I really did not have time to present our outcomes stratified by the type of mechanical circulatory support device, that is, intraaortic balloon pump, ventricular assist device, and ECMO (extracorporeal membrane oxygenation). Nevertheless, I agree with you that modern ventricular assist devices have outcomes much better than ECMO when used for bridge to transplantation.

This series of patients includes only two children supported with the Berlin Heart prior to transplantation; however, our initial experience with the Berlin Heart has been quite good, and even better than with previous forms of ventricular assist devices. So, I agree with you completely that ventricular assist devices are preferable to ECMO for bridge to transplantation, and that the use of ventricular assist devices, and especially the Berlin Heart in small children, infants, and neonates, should decrease wait list mortality.