Pediatric heart transplantation: 23-year single-center experience

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Abstract

Objective: Early and late mortality have significantly improved during recent decades in pediatric patients after heart transplantation (HTx). Nevertheless early and late morbidity and mortality are influenced by acute rejection, cardiac allograft vasculopathy (CAV), malignancy, renal failure, and graft failure. Methods: We evaluated our results after HTx in children under the age of 18 years with 23 years of follow-up. Perioperative characteristics, probability of survival, and time-related morbidity were retrospectively analyzed. Results: We included 169 pediatric HTx recipients, transplanted between 05/1986 and 05/2010. One hundred and one were males with a median age of 8.7 (0.02–23.2) years at the time of HTx. Main preoperative diagnoses were cardiomyopathy (CMP) (n = 139) with a median survival of 7.0 (0–23.2) years and congenital heart disease (CHD) (n = 30), median survival 11.3 (0–19.9) years. Overall survival at 1, 5, 10, and 15 years was 87%, 76%, 68%, and 50%, respectively. Patient survival was significantly reduced in patients with 0–1 year at the time of HTx versus 1–10 and 11–18 years: 2.3 (0–13.2) years versus 1–10 years = 8.6 (0–23.2) years; 11–18 years = 5.9 (0.003–18.5) years. Fifty-one patients were on mechanical circulatory support as a bridge-to-HTx with increased early but not late mortality. Ten patients underwent retransplant due to acute or chronic graft failure after a median posttransplant time of 12.25 (0.3–17.45) years. Late mortality was influenced by rejection, infection, posttransplant lymphoproliferative disease (PTLD) (11.8%), or CAV with an incidence of 25% at 5 years, 50% at 10 years, and approximately 75% at 15 years. Conclusions: Pediatric HTx is a safe and effective treatment for terminal heart failure. In our experience, there is no adverse effect of previous cardiac assist device implantation in long-term follow-up. Virtually all anatomic malformations are amenable to orthotopic HTx. Significant progress has been achieved in controlling rejection through improved immunosuppression and noninvasive rejection monitoring.

Keywords: Heart transplantation; Pediatric; Cardiac allograft vasculopathy; Acute rejection; PTLD; Survival; 23 years

1. Introduction

Kantrowitz and associates were the first to perform heart transplantation (HTx) in a 17-day-old child with a severe form of Ebstein anomaly [1]. The advent of pediatric HTx took place on 6 December 1967 at Maimonides Medical Center in Brooklyn, New York. Although this child survived for only 6.5 h, the technical feasibility of cardiac transplantation in infants could be demonstrated. More than 8000 pediatric heart transplantations have been performed since then [2]. Improvements in survival have made transplantation an established treatment option for pediatric patients with end-stage heart failure [2,3]. Today, pediatric heart transplant recipients benefit from reduction of early mortality by refinement of donor management, clear-cut indications for transplantation, improvements in perioperative management, and improved immunosuppressive regimens [3]. Also, ventricular assist device (VAD) therapy as bridge-to-HTx extends the period of survival time before a donor heart is received. However, uncertainty still exists about the causality and the prevention of late mortality, which depends on the occurrence of cardiac allograft vasculopathy (CAV) and graft failure, posttransplant lymphoproliferative disease (PTLD), infection, or rejection [2,4].

The objective of this study was to analyze the variables affecting both early and late mortality during 23 years of experience in pediatric HTx at a single institution.
2. Materials and methods

2.1. Patients

We retrospectively reviewed the charts of all pediatric patients below 18 years of age who underwent HTx between 1986 and 2010.

2.2. Heart transplantation

We performed blood group A, B, O-compatible transplantation in all patients; in the majority of patients, bilateral, and since 2005, also bicaval anastomoses were used. Additionally, a biventricular pacemaker with epicardial leads on the left ventricle (LV) and right ventricle (RV) was implanted in order to detect acute rejection, as previously described [5].

2.3. Induction therapy and rejection treatment

After HTx all patients received induction therapy during the first 2–3 days, consisting of steroid pulse therapy with methylprednisolone (Urbason®), mainly with two doses of a polyclonal lymphocyte or thymocytic antibody preparation (Tecelac®, Biotest; ATG-Fresenius®), Fresenius or Thymoglobulin®, Genzyme). Eight patients (after 2004) received the interleukin-2 receptor antibody basiliximab (Simulect®, Novartis) as induction therapy. Rejection treatment consisted of methylprednisolone pulse therapy either without ATG or with — one to five cycles of ATG in the case of acute cellular rejection (International Society of Heart and Lung Transplantation (ISHLT) above 2B or moderate) [6].

2.4. Immunosuppression

Immunosuppressive therapy consisted of triple-drug immunosuppression in the majority of patients during the first year. Patients with transplantation before 2000 received cyclosporine A (CyA), azathioprine (Aza), and steroids. Patients transplanted after 2000 received either CyA or CyA and mycophenolate mofetil (MMF) in addition to steroids. One-third of the patients received CyA in combination with Aza, MMF, or Everolimus (Cirtican®) after 2004. Nearly 80% of the patients received antiviral prophylaxis after transplantation with oral aciclovir for 4—8 weeks or temporarily ganciclovir in the case of Cytomegalovirus mismatch or infection.

2.5. Endomyocardial biopsy harvest and histopathological studies

Biopsies were harvested and tissues prepared in accordance with standard clinical practice as described before [5,7]. Rejection was graded according to the ISHLT grading system as described by Billingham and Stewart et al. [6].

2.6. Epicardial CAV

Biplane selective angiograms (15–30 frames/s) of coronary arteries were acquired digitally with standard biplane angiographic X-ray equipment (INTEGRIS/ LARC system, Philips Medical Systems, Nederland) using a nonionic contrast agent and were stored in The Digital Imaging and Communications in Medicine format. CAV was scored from angiograms according to the Stanford criteria [7,8].

2.7. Statistical analysis

Data are expressed as median (range) or mean values ± SD (standard deviation) for continuous variables and as frequency with percentage for categorical variables. Differences between median/mean were tested by unpaired Mann–Whitney test and Wilcoxon test for numerical data without normal distribution. Cumulative survival curves were constructed according to the Kaplan–Meier methods. A log-rank test was used to compare survival between groups with a hazard ratio (odds ratio as an estimate of risk). A p < 0.05 was considered significant. Data were analyzed with Prism for Macintosh, release 4 (GraphPad Software, San Diego, USA) and SPSS for Windows, release 10 (SPSS Inc., Chicago, IL, USA).

3. Results

3.1. Patient population

We included 169 patients in this analysis. Twenty-two (13%) patients were 0—1 year, 26 (15%) patients 1—3 years, 19 (11%) patients 3—6 years, 18 (10%) patients 6—10 years, and 84 (49%) patients were 10—18 years of age at the time of transplantation. One hundred thirty-nine patients were transplanted due to end-stage heart failure caused by cardiomyopathy or myocarditis: 114 had dilative disease, 10 hypertrophic with or without obstruction, nine restrictive, and six had status post myocarditis, see Table 1. Thirty patients received transplantation for end-stage heart failure due to congenital heart disease (CHD); see Table 1. In the CHD group 21/30 (70%) had previous cardiac surgery, with single ventricle physiology in 13/30 (43%). Previous surgery included aortopulmonary shunt (n = 8), Partial cavo-pulmonary anastomosis (n = 4), and Total cavo-pulmonary anastomosis (n = 3), Mustard procedure (n = 2), Senning procedure (n = 2), AKR or Ross procedure (n = 2). Twelve of the 17 surgical procedures were performed outside the Deutsches Herzzentrum Berlin. Eight out of 17 patients had two or more surgical procedures prior to HTx. Mean age at the time of HTx was 8.8 (0.02—17.9) years.

<table>
<thead>
<tr>
<th>Cardiomyopathy (CMP) (n = 139)</th>
<th>Congenital heart disease (n = 30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dilatative</td>
<td>TGA (n = 114 (82%))</td>
</tr>
<tr>
<td>Hypertrophic</td>
<td>ccTGA (n = 10 (7.2%))</td>
</tr>
<tr>
<td>Restrictive</td>
<td>HLHS (n = 9 (6.5%))</td>
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<tr>
<td>Post myocarditis</td>
<td>TA (n = 6 (4.3%))</td>
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<tr>
<td></td>
<td>AS (n = 2) 7%</td>
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<tr>
<td></td>
<td>CAVSD (n = 2) 7%</td>
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<tr>
<td></td>
<td>Other (n = 9) 28%</td>
</tr>
<tr>
<td></td>
<td>Single ventricle (n = 13) 43%</td>
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<td></td>
<td>Two ventricles (n = 17) 57%</td>
</tr>
</tbody>
</table>

Table 1. Reasons for heart transplantation.
3.2. Overall survival

Nineteen patients survived for more than 15 years, 39 patients for more than 10 years, and 80 patients for more than 5 years during the 23-year follow-up period.

The median survival time for patients with CHD was 11.3 (0—19.9) years. Fifteen deaths occurred in patients with CHD during the follow-up period: 9/15 (60%) patients died within the first 30 days (early mortality: bleeding, acute graft failure, or acute rejection), 2/15 (13%) patients died in the period from 30 days to 1 year, and 4/15 (27%) patients died later than 1 year after transplantation (late mortality: CAV, Acute Rejection, Percutaneous transluminal coronary angioplasty, or graft failure).

The median survival time for patients with CMP/myocarditis was 7.0 (0—23.2) years. Forty-eight deaths (34.5%) occurred in patients with CMP/myocarditis during the 23 years of the follow-up period: 9/46 (6.5%) patients died within the first 30 days (early mortality: bleeding, acute graft failure, or acute rejection), whereas 6/46 (13%) patients died after 30 days and up to 1 year after transplantation and 31/46 (67%) patients died more than 1 year after HTx (late mortality: CAV, graft failure, acute rejection, PTLD, or infection). The cause of death could not be definitively elucidated in 9/49 (19%) patients. The long-term survival and relative risk ratio did not differ significantly between patients with CHD and CMP; see Fig. 1.

In relation to the different transplant periods 1986–1999 versus 2000–2010, early survival improved significantly in the later period, see Fig. 2. Early mortality (<30 days) was significantly higher in the early transplant period (1986–1999): 12/89 perioperative deaths during 1986–1999 versus 4/80 patients during 2000–2010.

According to the age at the time of transplantation, survival was significantly decreased in patients transplanted at an age of 0–1 year, see Fig. 3. Patients aged 1–10 years showed the best early and long-term survival; see Fig. 3.

3.3. VAD therapy

In 51 patients a ventricular assist device was implanted as a bridge-to-transplantation with a median support time of 37 (1—409) days; see Table 2. In 8/51 patients end-stage heart failure was related to CHD and in 43/51 patients to CMP. Long-term posttransplant mortality was not influenced by VAD therapy; see Fig. 4. Fifteen of the 51 patients with VAD died during the 23 years of follow-up. Six of the 15 patients died during the first week (mostly CHD patients) due to bleeding, acute graft failure, rejection, or infection; 3/51 patients died within a 6-month period after transplantation due to either rejection, infection, or PTLD and 6/51 after a median of 5.1 (1–16) years (rejection, CAV with graft failure, or PTLD). There was no significant difference in the median survival between patients without versus with VAD therapy as a bridge-to-transplantation: 13.1 (0–23.2) versus 16.1 (0–18.9) years; see Fig. 4.

Table 2. Ventricular assist device (VAD) and median support time in days.

<table>
<thead>
<tr>
<th>Number and Percent</th>
<th>Support Time (days)</th>
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<tbody>
<tr>
<td>LVAD (Berlin Heart®, Berlin, Germany)</td>
<td>26 (51%)</td>
</tr>
<tr>
<td>BWAD (Berlin Heart®, Berlin, Germany)</td>
<td>17 (33%)</td>
</tr>
<tr>
<td>ECMO (PediVAS®, Levitronix GmbH, Zürich, Switzerland)</td>
<td>4 (8%)</td>
</tr>
<tr>
<td>LVAD (Heart Ware®, Framingham, Massachusetts, USA)</td>
<td>3 (6%)</td>
</tr>
<tr>
<td>VAD pneumatic (Toyobo NCVC, Japan)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>All</td>
<td>51 (100%)</td>
</tr>
</tbody>
</table>
3.4. Acute rejection

Acute rejection was diagnosed by clinical status, echocardiography, or intramyocardial electrogram (IMEG) and was confirmed by RV biopsy. Twenty-four percent of all patients had no episode of rejection, 25% had one, 29% had 2–3 and 10% had more than four episodes of rejection; see Table 3. Rejection episodes occurred relatively early (18 vs 176 days after HTx) in patients with more than two episodes of rejection. Treatment was based on steroid pulse or ATG therapy, whereas patients with more than four rejection episodes received a mean of nine doses of ATG; see Table 3. In 20 (12%) patients no information could be obtained about the occurrence of rejection due to missing biopsy or clinical data. Acute rejection was a leading cause of early mortality in 5/19 patients and for late mortality in 8/46 patients.

3.5. Cardiac allograft vasculopathy

Cardiac allograft vasculopathy was detected in 47 transplanted hearts, but was absent in 39 and its incidence not known in 64 patients due to missing data or missing coronary angiograms. Freedom from CAV was 75% at 5 years, 50% at 10 years, and approximately 25% at 15 years. Freedom from CAV was 75% at 5 years, 50% at 10 years, and approximately 25% at 15 years. Focal stenosis was diagnosed in 23/47 (50%) patients with CAV, leading to interventional treatment in 12 patients (including Percutaneous transluminal coronary angioplasty or stent implantation). A statin was given if CAV was detected in patients older than 10 years of age, but not on a prophylactic basis. Survival was influenced by diagnosis of CAV; see Fig. 5. CAV was the reason for retransplantation in 10 patients after a median posttransplant time of 12.25 (0.3–17.45) years, where mortality reached 50% for the first year after re-HTx. In four of five surviving patients, kidney transplantation was performed simultaneously and posttransplant survival was 4.7 (3.6–6.4) years.

3.6. PTLD

Twenty out of a total of 169 (11.8%) patients developed PTLD with a relevant association to the Epstein–Barr virus (EBV) [9,10]. Median posttransplant time for primary diagnosis was 3.0 (0.2–12.8) years. Eight of the 20 patients died after a median posttransplant time of 6.2 (1.05–16.1) years, which meant that PTLD was responsible for 4.7% of the overall mortality.

3.7. Renal failure

Chronic renal failure (more than 1 year posttransplant) was diagnosed in 49 patients, was absent in 89 patients, and data were not available in 31 patients who died either within the first 30 days or for unknown reasons out of the hospital. Five patients needed chronic hemodialysis. Mean creatinine was 1.9 ± 0.8 mg dl⁻¹ in patients with renal failure versus 0.86 ± 0.4 mg dl⁻¹ in patients without.

4. Discussion

Heart transplantation is a well-established treatment option for infants and children with end-stage heart failure due to complex congenital cardiac defects or cardiomyopathy [4,11–14]. We report our 23-year single-center experience in HTx in children under the age of 18 years. During a 23-year follow-up period, a total of 104/169 (61%) patients survived a median time of 7.9 (0.3–23.2) years; 65 patients died during the follow-up period after a median time elapse of 18.5 (0–17.6) years. Our mortality rate is comparable to that of other published studies with long-term survival (up to 20-year follow-up period) in which mortality rates of 25–44% have been described [4,13,15].

4.1. Early mortality

Early mortality was recorded in 19 out of 169 (11.8%) patients. Early mortality was caused by bleeding, acute graft failure, infection, acute fulminant rejection, or multi-organ failure [4,16]. We found, in accordance with the literature,
that acute graft failure related to acute rejection may be associated with previous cardiac surgery [17,18]. Early mortality is significantly influenced by the preoperative diagnosis, where eight of 19 patients with early mortality were patients with CHD [2,15,16]. Age under 1 year was also identified as a risk factor for early mortality [2,15,16]. Reduction of early mortality may have been achieved with the introduction of Human leucocyte antigen screening, cross-match and evaluation of the donor by echocardiography, clinical status, or other underlying illness including infectious problems [19]. Patients without optimal condition for HTx, for example, with borderline pulmonary vascular resistance (PVR), should be considered for VAD therapy. PVR might then be responsive to left ventricular unloading therapy and/or additional drug therapy (including therapy of pulmonary arterial hypertension (PAH) prior to transplantation). VAD therapy in patients with end-stage heart failure may also reduce early mortality due to improvement of organ function and prevention of multi-organ failure before transplantation. Indicators of organ dysfunction should be excluded by laboratory tests, where a progressive rise of liver- (Aspartate transaminase, Alanine transaminase, and bilirubin) or kidney-function (creatinine and urea) parameters might be indicative for VAD therapy. Especially in those patients, who were already receiving a maximum of anti-congestive treatment.

The perioperative management includes treatment of pulmonary arterial hypertension (PAH) with Nitric oxide (NO) dilators to prevent postoperative right heart failure of the graft.

Improvements in immunosuppression and the introduction of new types (1996 MMF, 1989 Sirolimus, and 1997 Everolimus) have also contributed to decreased early and late mortality. Today, it is possible to choose the most effective immunosuppressive combination and to individually adapt it to the needs of the patient. We still use induction therapy and a triple immunosuppressive therapy for the first year as a minimum. In patients with recurrent rejection we continue with steroids 1 year after transplant. Change of calcineurine inhibitor (CNI) or antimetabolite might also be indicated in accordance with the risk or tolerance of each patient or in patients with recurrent rejection, side-effects, metabolization problems, or drug intolerance.

With the improvements in monitoring rejection by IMEG, echocardiography and laboratory tests, we were able to more effectively identify and treat patients with acute rejection [5,20]. Early mortality was also increased in patients with VADs according to the increased risk of bleeding from multiple reoperations and extensive anticoagulation therapy during VAD therapy or risk of rejection from VAD therapy and blood transfusion [21]. Because rejection rates might be increased in VAD patients due to reactive antibodies (PRA) sensitized from VAD and repeated transfusion, perioperative screening for these antibodies is important, especially with the suspicion of rejection. Patients with bleeding problems may be managed similarly to other perioperative patients with stabilization of hemostasis. The highest risk (up to 30%) for early mortality was observed in patients with congenital heart disease and VAD therapy.

4.2. Late mortality

Late mortality was detected in 46/169 (27%) patients and was due to acute or chronic graft failure (including CAV), infection or PTLD [13,15]. Late mortality did not differ significantly between patients with CHD and CMP [13,15,16]. Pediatric patients requiring a VAD prior to HTx had a long-term survival similar to that of patients not receiving any mechanical circulatory support; see Fig. 2 [22]. Due to the shortage of pediatric donor hearts, VAD therapy, with the development and use of the Berlin Heart® since 1990, has become a valuable tool to bridge even small children to transplantation and to cover the time until a suitable heart is available [22]. Long-term survival is not influenced by VAD therapy [12,22].

4.3. CAV

CAV with chronic graft failure has a major impact on survival and showed a time-related increase, if posttransplant time exceeds 10 years. According to previous studies the rate of CAV might be related to the screening methods used in individual institutions [7]. In our institution the detection of CAV has been established and new definitions and diagnostic criteria have been published previously [7]. CAV was the main cause for re-transplantation, but frequency was low (5.9% of all patients during 23-year follow-up). Mortality is high (up to 50%) in patients undergoing retransplantation [23]. CAV may be influenced by statin therapy, although appropriate studies are lacking especially in the pediatric age group and the impact of lipid abnormalities remains controversial.

4.4. PTLD

The incidence of PTLD was 11.8% in our cohort. Eight patients died 3 years after primary diagnosis of PTLD despite specific treatment including reduction of immunosuppression, rituximab (CD20-antibody), or chemotherapy. Details of diagnosis and therapy of patients with PTLD have been described previously [9]. Malignancy and infection (bacterial or viral) may give rise to 5–15% of mortality, with an increasing risk for patients who survived more than 5 years after HTx [2,9]. After identification of risk factors for PTLD, we tried to avoid polyclonal lymphocyte or thymocytic antibody preparation (Tecelac®, Biotest; ATG-Fresenius®, Fresenius or Thymoglobuline®, Genzyme) for induction therapy [9,10]. Since 2000, we preferred MMF and since 2004 mTOR-inhibitors (Everolimus) instead of Azathioprin as maintenance therapy. And we introduced tumor screening for our patients, including viral load monitoring in order to identify early and treat patients at risk of PTLD [9].

4.5. Acute rejection

Acute rejection was absent in 24% of the patients. The first rejection episode occurred earlier in patients with two or more rejection episodes and later in patients with only one. Acute rejection was the cause of death in 13 of 169 patients, although the reason for death was missing in the data for some patients who died outside the hospital. With the use of
the IMEG system for rejection monitoring, acute rejection treatment was started early and the incidence of RV biopsy and severe rejection could be reduced [5]. Early treatment of rejection may be important in order to prevent the development of CAV [7]. An increased risk for acute cellular or humoral rejection after exposure to multiple blood transusions or VAD therapy prior to transplantation has been described [21,24]. Therefore, acute rejection is still influencing early and late mortality, especially with its impact on the development of CAV [4,21].

The introduction of new immunosuppressive agents during the last decade, that is, MMF and the mTOR-inhibitors everolimus and sirolimus, play an important role in preventing acute, chronic rejection and the development or progression of CAV. Especially mTOR-inhibitors may pave the way for adaptation of CNI dosage, which influences the outcome of pediatric patients at pronounced risk for 'over-immunosuppression' [25]. Reducing overall immunosuppression might reduce specific side effects, for example PTLD or immunosuppression [25]. Reducing overall immunosuppression, might reduce specific side effects, for example PTLD or immunosuppression [25]. Reduced overall immunosuppression might reduce specific side effects, for example PTLD or immunosuppression [25]. Further studies and especially randomized controlled pharmacological trials are needed to gather more information about the use of different immunosuppressive regimens in pediatric HTx patients.

References


Appendix A. Conference discussion

Dr. R. Di Donato (Rome, Italy): At Bambino Gesu’ Hospital in Rome we have a very similar experience. We started in 1986 and performed transplants in 183 patients with an overall survival of 66%. So the series are very similar. There are some little differences, and I will relate to those with a few questions.

In our series, follow-up is 100% complete, whereas I noticed that you report 9 late deaths due to unknown causes because of ‘lost to follow up’. That is 20% of the late deaths in your series.

My first question is, do you think there is an issue of poor compliance to therapy that might have, though moderately, affected your results?

Dr. Huébler: The follow-up of these patients may be influenced by their origin, and there we lost track of the patients.
Dr Hübner: We get patients from all over Germany for cardiomyopathies because we had the opportunity to support the children with a ventricular assist device. That is one major source of patients with cardiomyopathy.

In our experience, the incidence of postcardiotomy emergency transplantation is going down.

Dr Di Donato: You found a greater risk for heart transplantations performed in patients under one year of age. Conversely, the long-term survival of the same group of patients seems better than in patients transplanted at an older age. In fact, similar survival trends have been repeatedly reported by the Loma Linda center.

As a third question, can you comment on this data? Is there an early surgical risk involved in the younger age group?

Dr Hübner: I think it is a common observation that younger patients do worse than the older age groups. It is surgically more challenging, and also I think we have, especially in very young patients, assistive device therapy. In this subset of patients, I think it is more challenging to perform transplantation.

Dr H. Ichikawa (Osaka, Japan): My question concerns PTLD mentioned in one slide. I think in pediatric transplantation, it is key to improving long-term survival.

So do you regularly measure EB virus, and also, if so, when do you start to treat PTLD?

Dr Hübner: We measure EBV load early, and as I mentioned, we deliberately use antiviral therapy. I agree that it is a major problem for long-term results, but as you saw, it is 20 patients out of 169.

Dr R. Przybylski (Zabrze, Poland): Just one very brief question, because this is one of the biggest European centers. What is your experience in regard to the age mismatch in donor-recipients?

Dr Hübner: We deliberately use different sizes, and in my experience, I would accept patient hearts 100% bigger than the recipient. That is for me a sort of cut-off. We use echocardiographic measurements to check the size of the heart.