Pediatric Heart Transplantation: Report from a Single Center in China

Fei Li, Jie Cai, Yong-Feng Sun, Jin-Ping Liu, Nian-Guo Dong
Department of Cardiovascular Surgery, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei 430022, China

Abstract

Background: Although heart transplantation (HTx) has become a standard therapy for end-stage heart diseases, experience with pediatric HTx is limited in China. In this article, we will try to provide the experience with indications, complications, perioperative management, immunosuppressive therapy, and survival for pediatric HTx based on our clinical work.

Methods: This is a retrospective chart review of the pediatric patients undergoing HTx at Department of Cardiovascular Surgery of Union Hospital from September 2008 to December 2014. We summarized the indications, surgical variables, postoperative complications, and survival for these patients.

Results: Nineteen pediatric patients presented for HTx at Union Hospital of Tongji Medical College, of whom 10 were male. The age at the time of transplantation ranged from 3 months to 18 years (median 15 years). Patient weight ranged from 5.2 kg to 57.0 kg (median 38.0 kg). Pretransplant diagnosis included cardiomyopathy (14 cases), complex congenital heart disease (3 cases), and tumor (2 cases). All recipients received ABO-compatible donor hearts. Postoperative complications occurred in 12 patients, including cardiac dysfunction, arrhythmia, pulmonary infection, renal dysfunction, and rejection. Two of them experienced cardiac failure and required extracorporeal membrane oxygenation. The immunosuppression regimen was comprised of prednisone, a calcineurin inhibitor, and mycophenolate. All patients recovered with New York Heart Association (NYHA) Class I–II cardiac function and were discharged. Only one patient suffered sudden death 19 months after transplantation.

Conclusion: Orthotopic HTx is a promising therapeutic option with satisfying survival for the pediatric population in China with end-stage heart disease.

Key words: China; Complications; Indications; Pediatric Heart Transplantation; Survival

Introduction

Pediatric heart transplantation (HTx) has become a successful treatment option for children with end-stage heart failure, with long-term survival attributed to advances in surgical techniques and immunosuppression regimens. Since Adrian Katrowitz performed the first pediatric HTx in 1967, more than 500 pediatric HTx are performed annually, mostly in Europe and North America.[1] However, experience with pediatric HTx from China is limited. In this study, we reported the 19 pediatric HTx at Union Hospital of Tongji Medical College, and try to explore the indications, complications, perioperative management, immunosuppressive therapy, and survival for pediatric HTx in China.

Methods

This study was approved by the Ethics Committee and performed in accordance with the ethical standards of the Declaration of Helsinki. All of the subjects recruited for the study provided written informed consent. Data were collected for HTx patients who were aged ≤18 years old at the time of transplantation from September 2008 to December 2014 at Union Hospital of Tongji Medical College. We summarized demographic data, pretransplant clinical history, surgical parameters, donor information, postoperative complications, and survival for these patients.

Address for correspondence: Dr. Nian-Guo Dong, Department of Cardiovascular Surgery, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, 1277 Jiefang Avenue, Wuhan, Hubei 430022, China
E-Mail: dongnianguo@hotmail.com

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early postoperative management and complications, mortality, and immunosuppressive regimens for these recipients. Since endomyocardial biopsy was not performed at our institute, the diagnosis of rejection was based on clinical symptoms such as irritability, fatigue, heart failure, arrhythmias, electrocardiographic, and echocardiographic changes.

Descriptive data were presented as the mean ± standard deviation (SD) or median, as appropriate. Student’s t-test was used to determine statistical significance. Logistic regression analysis was carried out to assess the impact of ischemic time on ventilation time, Intensive Care Unit (ICU) stay, and hospitalization time after operation. The SPSS 17.0 software (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. A $P < 0.05$ was considered to be statistically significant.

**Results**

**Patients’ demographics**

Nineteen pediatric patients underwent HTx at Union Hospital of Tongji Medical College, and one patient is still in the hospital now. The age at the time of transplantation ranged from 3 months to 18 years (mean 12.6 years old, median 15 years old). There were 10 male recipients. Patient weight ranged from 5.2 kg to 57.0 kg (mean 35.0 kg, median 38.0 kg). Pretransplant diagnosis included cardiomyopathy 14 cases (73.7%), complex congenital heart disease (CHD) 3 cases (15.8%), and tumor 2 cases (10.5%). The echocardiographic diagnosis for the first CHD recipient was visceras in versus, asplenia syndrome, totally anomalous pulmonary venous connection (supracardiac type), complete atrioventricular septal defect (Rastelli A type) with severe common atrioventricular valve regurgitation, single atrium, left ventricular dysplasia, double outlet of right ventricle, and pulmonary stenosis. The diagnosis for the second was dextrocardia, complete atrioventricular septal defect (Rastelli C type) with severe common atrioventricular valve regurgitation, single atrium, single ventricle, pulmonary stenosis and dextro aortic arch. The third was right ventricular hypoplasia syndrome, patent ductus arteriosus, tricuspid valve dysplasia with ebstein anomaly, pulmonary atresia with intact ventricular septum (PA‑IVS) associated with right‑ventricular dependent coronary circulation (RVDCC). Postoperative pathological diagnosis of the two patients with tumor were infiltrating lipoma involving left and right ventricle and low‑grade myofibroblastic sarcoma in left atrium, respectively. Two patients had cardiac surgery, and one had exploratory thoracotomy surgery prior to HTx. All the patients had New York Heart Association (NYHA) Class IV heart failure prior to transplant. All the patients had panel reactive antibody (PRA)<10%, and received ABO‑compatible donor hearts. Donor/recipient (D/R) weight ratio ranged from 0.7 to 2.7 (mean 1.6, median 1.5) [Table 1].

**Surgical parameters**

The total donor graft ischemic time ranged from 106 min to 490 min (mean 267.9 min, median 150 min). The cardiopulmonary bypass (CPB) time ranged from 71 min to 217 min (mean 123.4 min, median 112 min). Seventeen patients underwent biatrial anastomosis; two patients underwent bicaval anastomosis for anomalous pulmonary venous connection and dextrocardia. Three patients left the operating room with delayed chest closure, and two of these

| Table 1: Characteristics of the 19 patients undergoing HTx |
|-------------|-----------|-----------|----------------|------------------|-----------|---------|----------|------------------|
| Number | Gender | Age (years) | Weight (kg) | Operation date | Pretransplant diagnosis | Mean PAP (mmHg) | EF (%) | D/R blood type | D/R weight ratio |
| 1 | Male | 18 | 45.5 | 5/9/2008 | DCM | 44 | 20 | AB–AB | 1.5 |
| 2 | Male | 18 | 45.0 | 28/11/2008 | DCM | 20 | 28 | O–O | 1.1 |
| 3 | Male | 16 | 56.0 | 11/6/2009 | DCM | – | 31 | O–AB | 1.2 |
| 4 | Male | 16 | 51.0 | 10/7/2009 | DCM | – | 18 | O–O | 1.1 |
| 5 | Male | 13 | 45.0 | 20/11/2009 | DCM | 22 | 19 | A–A | 1.4 |
| 6 | Female | 15 | 40.0 | 28/11/2010 | RCM | 35 | – | O–O | 1.8 |
| 7 | Male | 16 | 57.0 | 14/12/2011 | DCM | 48 | 38 | A–A | 1.2 |
| 8 | Female | 16 | 38.0 | 7/9/2012 | Tumor | – | 72 | O–O | 1.6 |
| 9 | Male | 18 | 50.0 | 15/8/2013 | CHD | 32 | 19 | B–B | 1.4 |
| 10 | Male | 11 | 28.0 | 7/3/2014 | DCM | 26 | 16 | B–AB | 2.7 |
| 11 | Female | 11 | 26.0 | 30/3/2014 | CHD | 30 | – | B–B | 2.5 |
| 12 | Female | 14 | 36.0 | 16/5/2014 | HCM | 46 | 38 | O–O | 1.8 |
| 13 | Female | 18 | 29.0 | 6/8/2014 | DCM | 27 | 29 | A–A | 1.7 |
| 14 | Female | 8 | 21.0 | 21/9/2014 | HCM | – | 56 | A–A | 0.7 |
| 15 | Male | 10 months | 7.5 | 23/9/2014 | DCM | – | 15 | O–O | 1.7 |
| 16 | Female | 6 | 18.0 | 28/9/2014 | DCM | – | 26 | O–O | 0.7 |
| 17 | Female | 17 | 49.0 | 21/10/2014 | LA tumor | 52 | 51 | B–B | 1.2 |
| 18 | Female | 8 | 18.0 | 20/11/2014 | DCM | 25 | 64 | O–O | 2.3 |
| 19 | Male | 3 months | 5.2 | 22/11/2014 | CHD | – | 70 | B–B | 2.7 |

HTx: Heart transplantation; D: Donor; R: Recipient; PAP: Pulmonary arterial pressure; EF: Ejection fraction; DCM: Dilated cardiomyopathy; RCM: Restrictive cardiomyopathy; HCM: Hypertrophic cardiomyopathy; CHD: Congenital heart disease; LA: Left atrial.
three patients experienced cardiac failure following HTx requiring extracorporeal membrane oxygenation (ECMO). In both patients, cannulation was achieved via a transthoracic approach in the operation room. A centrifugal pump was utilized due to smaller size and the ease of deployment. ECMO was withdrawn 74 h and 115 h later, respectively. The third patient required delayed closure because the pericardial cavity was not enough for a large donor heart [Table 2].

**Table 2: Surgical characteristics of 19 patients**

| Number | Ischemic time (min) | Surgical type | CPB time (min) | Delayed chest closure | Mechanical circulatory support |
|--------|---------------------|---------------|----------------|-----------------------|-----------------------------|
| 1      | 106                 | Biatrial      | 138            | No                    | No                          |
| 2      | 120                 | Biatrial      | 86             | No                    | No                          |
| 3      | 133                 | Biatrial      | 96             | No                    | No                          |
| 4      | 119                 | Biatrial      | 97             | No                    | No                          |
| 5      | 127                 | Biatrial      | 104            | No                    | No                          |
| 6      | 154                 | Biatrial      | 113            | No                    | No                          |
| 7      | 150                 | Biatrial      | 112            | No                    | No                          |
| 8      | 442                 | Biatrial      | 117            | No                    | No                          |
| 9      | 388                 | Bicaval       | 201            | No                    | No                          |
| 10     | 121                 | Biatrial      | 71             | No                    | No                          |
| 11     | 248                 | Bicaval       | 174            | No                    | No                          |
| 12     | 139                 | Biatrial      | 86             | No                    | No                          |
| 13     | 490                 | Biatrial      | 114            | No                    | No                          |
| 14     | 452                 | Biatrial      | 217            | Yes                   | ECMO 74 h                   |
| 15     | 379                 | Biatrial      | 97             | Yes                   | ECMO 115 h                  |
| 16     | 130                 | Biatrial      | 90             | No                    | No                          |
| 17     | 482                 | Biatrial      | 179            | No                    | No                          |
| 18     | 522                 | Biatrial      | 107            | No                    | No                          |
| 19     | 388                 | Biatrial      | 146            | Yes                   | No                          |

CPB: Cardiopulmonary bypass; ECMO: Extracorporeal membrane oxygenation.

**Postoperative management**

Postoperative time to first extubation ranged from 15 h to 348 h (median 24 h). ICU stay ranged from 3 days to 35 days (mean 13.5 days, median 7 days). Since isolation ward were not available until 2010, ICU stay was longer. Inotropic support after operation ranged from 1 day to 12 days (mean 5.2 days, median 5 days). Postoperative complications occurred in 12 patients, including cardiac dysfunction (4 cases), arrhythmia (3 cases), pulmonary infection (6 cases), renal dysfunction (2 cases), and rejection (3 cases). Among the four patients with heart failure, two required ECMO in the operation room due to difficulty in weaning off CPB. The other two suffered heart failure after surgery, with clinical manifestations of low blood pressure, high central venous pressure, tachycardia, clammy extremities, edema, and decreased exercise tolerance. For these two patients, inotropic agents, nesiritide, diuretics, beta blockers, and vasodilators were used in combination. Frequent atrial fibrillation and ventricular premature beats were the most common type of arrhythmias observed in the recipients. After excluding cardiac structure abnormality by echocardiography, we increased the dose of anti-rejection drugs and amiodarone as symptomatic therapy. Then the rhythm converted to sinus rhythm. Two patients required peritoneal dialysis in the immediate postoperative period and both experienced a full recovery of renal function. All patients achieved a postoperative EF value of at least 50% and had NYHA Class I–II cardiac function prior to discharge. All the patients returned for follow-up care, and the length of follow-up ranged from 1 month to 70 months. One patient suffered sudden death, 19 months later after discharge. The patient probably died of primary graft failure [Table 3].

**Table 3: Postoperative characteristics and survival of 19 patients**

| Number | Ventilation time (h) | ICU stay (days) | Inotropic support time (days) | Complications | EF 3 weeks after operation (%) | Hospitalization time after operation (days) | Survival status |
|--------|----------------------|----------------|-------------------------------|---------------|--------------------------------|---------------------------------------------|----------------|
| 1      | 25                   | 33             | 6                             | HF, pneumonia, rejection | 67               | 42                           | Deceased         |
| 2      | 18                   | 35             | 3                             | Pneumonia     | 65               | 46                           | Alive            |
| 3      | 18                   | 31             | 6                             | Arrhythmia    | 62               | 50                           | Alive            |
| 4      | 20                   | 29             | 4                             | No            | 67               | 34                           | Alive            |
| 5      | 42                   | 25             | 6                             | Arrhythmia, rejection | 70               | 37                           | Alive            |
| 6      | 24                   | 7              | 6                             | Pneumonia     | 63               | 34                           | Alive            |
| 7      | 28                   | 4              | 5                             | rejection     | 74               | 27                           | Alive            |
| 8      | 24                   | 5              | 5                             | No            | 70               | 20                           | Alive            |
| 9      | 22                   | 7              | 6                             | Arrhythmia    | 74               | 58                           | Alive            |
| 10     | 19                   | 7              | 1                             | No            | 78               | 26                           | Alive            |
| 11     | 19                   | 9              | 1                             | HF            | 59               | 43                           | Alive            |
| 12     | 16                   | 7              | 6                             | No            | 66               | 25                           | Alive            |
| 13     | 36                   | 3              | 3                             | No            | 77               | 21                           | Alive            |
| 14     | 348                  | 9              | 12                            | HF            | 59               | 29                           | Alive            |
| 15     | 312                  | 21             | 5                             | HF, pneumonia, renal dysfunction | 62               | 84                           | Alive            |
| 16     | 15                   | 3              | 4                             | No            | 62               | 23                           | Alive            |
| 17     | 35                   | 7              | 8                             | No            | 70               | 27                           | Alive            |
| 18     | 112                  | 6              | 3                             | Pneumonia     | 65               | 36                           | Alive            |
| 19     | 164                  | 9              | 9                             | Pneumonia, renal dysfunction | –                | –                            | Hospital stay    |

ICU: Intensive care unit; HF: Heart failure; EF: Ejection fraction.
**Immunosuppression protocol**

Interleukin-2 receptor antagonist (IL-2RA, basiliximab) was used for induction therapy in all recipients. The first dose (20 mg for children <35 kg, 40 mg for children ≥35 kg) was administered intravenously 2 h prior to the operation. The second dose was administered intravenously 4 days after transplantation. Maintenance immunotherapy consisted of cyclosporine, mycophenolate, and prednisone before 2011, while triple therapy of tacrolimus, mycophenolate, and prednisone were used from 2011 onward. One of the advantages of new regimens was reduced occurrence of side-effects such as nephrotoxicity, hepatotoxicity, hirsutism, gingival hyperplasia, nausea, and diarrhea.

**Overview of heart transplantation at our institution**

A total of 203 cases of HTx were performed at our center since September 2008, and 84 of those cases were performed in 2014. The proportion of pediatric HTx in 2014 has increased compared to the past (11.9% vs. 7.6%). Moreover, pediatric HTx were performed at a younger age (9.40 ± 6.06 years vs. 16.20 ± 1.64 years, t = 3.258, \(P = 0.005\)) and a lower weight (23.77 ± 12.99 kg vs. 47.50 ± 6.55 kg, \(t = 4.932, P < 0.001\)) [Figure 1]. Another breakthrough was the successful HTx in two infants. One of these infants was 3 months old, perhaps the youngest heart transplant recipient in China’s history. The baby was diagnosed with PA-IVS associated with RVDCC.

**Discussion**

Pediatric HTx has continued to evolve since a case reported in 1967. With advances in surgical strategies and medical therapies, the outcomes have greatly improved. However, pediatric HTx in China is still in its infancy, and there is still much to explore. The present article retrospectively analyzed surgical indications, perioperative management, complications, and short-term survival at our center.

Dilated cardiomyopathy is the most common indication for pediatric HTx at our center, which was consistent with the data from the registry of the International Society for Heart and Lung Transplantation (ISHLT). The incidence of dilated cardiomyopathy is 0.58 per 100,000 children and accounts for over 50% of cardiomyopathy in the USA. However, pediatric DCM in China lacks large-scale epidemiological survey. Patients with DCM have relatively low waitlist mortality. Towbin et al. reported that freedom from death or transplantation at 1 and 5 years after DCM diagnosis was 69% and 54%, respectively. DCM patients submitted to HTx underwent the surgery at our center at relatively older age, except for one infant. The surgical correction and palliation in children with CHD has improved significantly. Moreover, 3-month posttransplant survival for children with a diagnosis of CHD has been reported worse than children with cardiomyopathy. Single-center studies also demonstrated an increase in perioperative mortality associated with neonatal age and pulmonary reconstruction. Therefore, primary transplant for CHD in which palliative operation is feasible is not recommended. Recently, we presented a 3-month-old infant with HTx, diagnosed PA-IVS associated with RVDCC, without an obvious symptom of cyanosis, but frequent episodes of heart failure. Palliation surgery may not be a good choice for him. A recent study also suggested early consideration of transplantation in PA-IVS patients with RVDCC.

The overall survival after HTx for the pediatric population is approximately 90% at 1 year. The survival rate during hospitalization is 100% at our center. All patients were followed after discharge. The follow-up time ranged from 1 month to 70 months. Only one patient suddenly died of primary graft failure, which accounted for more than half of death within the first 3 years after transplantation in the presence of rejection. Donor characteristics have been shown to affect pediatric HTx. While donor cause of death, inotropic agents use, and cardiopulmonary resuscitation were demonstrated less impact on outcomes than previously thought, longer ischemic time is still an important risk factor that can affect 1-year survival. Furthermore, the longer ischemic time has been associated with a longer period of ventilator dependence and longer stay in the ICU. However, the present study did not find an association among the above parameters, probably due to smaller patient numbers (data not shown).

Early postoperative management after pediatric HTx is crucial to success. Postoperative complications were closely associated with mortality during hospitalization and long-term survival. Cardiac dysfunction and pulmonary infection are the most common complications at our center. Infection accounts for approximately 12% of deaths during the 1st year after transplantation. Pathogens are typically bacterial, virus, and relatively uncommon fungus. One single-center study demonstrated that infants were more likely to experience more severe and chronic infection. Immunosuppression renders the receipts susceptible to infection, particularly with opportunistic agents. We need to find the balance between anti-rejection and anti-infection therapies. The ISHLT data have identified renal dysfunction as an important risk factor for 1-year pediatric heart transplant survival. Previous studies demonstrated the adverse effects of renal failure on perioperative graft loss. There were no occurrences of graft vascular disease or lymphoproliferative disease during the follow-up.

![Figure 1: Trend of pediatric heart transplantation at our institute.](Image)
Postoperative rejection-induced hemodynamic compromise can affect long-term survival. The endomyocardial biopsy is the gold standard for routine surveillance of cardiac allograft rejection. However, the diagnosis of rejection at our institute was performed mainly by clinical symptoms such as irritability, fatigue, heart failure, arrhythmias, electrocardiographic, and echocardiographic changes. Our immunosuppression protocol consisted of a calcineurin inhibitor and cytostatic. We originally used cyclosporine, but it has been replaced by tacrolimus due to its improved side-effect profile.

ECMO is the most feasible form of mechanical circulatory support and a practical option for pediatric HTx patients who are unable to wean from CPB or with the inadequate postoperative cardiac output. Vanderlaan et al. reported that both pre- and post-transplant use of ECMO was associated with an increased risk of perioperative graft loss. Two patients experienced cardiac failure following HTx requiring ECMO at our center. Both were cannulated via a transthoracic approach in the operation room after they could not be weaned from CPB. The ECMO support time was 74 h and 115 h, respectively. They both survived to hospital discharge. We regarded the posttransplant use of ECMO as a useful strategy for patients with graft dysfunction, allowing time for cardiac rest and gradual adaptation to a new hemodynamic environment. Another single-center retrospective study demonstrated that ECMO could provide effective hemodynamic support, improving postoperative survival as well. However, the sample size was small. We speculated that ECMO complications and precannulation end-organ condition may make it difficult to determine the positive effect of ECMO on survival. A larger multicenter study would be required to explore the effect of ECMO on postoperative survival.

Eighty-four HTx were implemented in our center in 2014, ranking first in China. The proportion of pediatric recipients <1-year old has increased gradually. Our study showed that short-term results of pediatric HTx at our institution were quite satisfactory and complication rates were acceptable. Relative to adults, pediatric heart transplant recipients still face greater organ shortages, and transplant operations can be more difficult due to technical difficulties imposed by some congenital malformations. Despite these disadvantages, pediatric HTx is a feasible and promising procedure in China. However, large registries and long-term survival remain to be assessed.

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Conflicts of interest
There are no conflicts of interest.

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