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ORIGINAL ARTICLE

Results of a national program of pediatric heart transplantation: strengths and weakness

Resultados de un programa nacional de trasplante cardiaco pediátrico: fortalezas y debilidades

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Abstract

Introduction: Pediatric heart transplantation is an effective therapy to treat advanced heart failure in children. **Objectives:** To analyze the immediate and mid-term results of pediatric patients listed for heart transplantation. **Material and Methods**: Registration of patients admitted to our transplant protocol between October 2001 and July 2016 were reviewed, analyzing demographic data, diagnosis, status at the time of listing, waiting time until transplantation, donor data, use of ventricular assist device, hemodynamic data, complications and global mortality. **Results:** Thirthy patients where included with a mean age of 9.4 years (1 month to 15 years). The most frequent diagnosis was dilated cardiomyopathy in 24 patients (80%). The status was I (urgency) in 19 cases and II in 11 cases. Ten patients died on the waiting list (33,3%) at an average of 52 days (13-139 days). Fourteen were transplanted (46.7%), with a waiting time of 199.6 days (4-586 days). Nine patients required mechanical support (30%). All patients received triple association of immunosuppression. One patient died 16 days post transplant due to primary graft failure (7.1%). The average follow-up was 43 months (0.5-159 months). Two patients died later on (82 and 55 months), both due to secondary rejection because of voluntary cessation of immunosuppressive therapy. Survival at 1 and 5 years was 93% and 74%, respectively. **Conclusions:** Our program has successfully transplanted 50% of patients enrolled, with good medium-term survival. A significant proportion of patients were listed urgently and 34.5% died on the waiting list.

Keywords:
Pediatric Heart transplantation,
Mechanical circulatory assist devices,
rejection,
immunosuppresive treatment,
waiting list

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Introduction

According to history, the first heart transplant was performed by Christian Barnard in an adult patient, on December 3 in 1967, in South Africa[1]. Three days later, Adrian Kantrowiz performed the second heart transplant in the United States, but this time was in a pediatric patient. The recipient was a newborn with severe Ebstein anomaly, receiving the heart from an anencephalic donor. Sadly, the patient survived only a few hours[2].

As Norman Shumway is considered the father of heart transplantation, due to his exhaustive work at Stanford University, Leonard Bailey worked with great effort focusing on the better development of pediatric cardiac transplantation at Loma Linda University, and therefore could be considered the father of pediatric heart transplantation. His initial interest was focused on those congenital heart diseases that were not susceptible to adequate surgical correction or palliation. On October 26th, 1984, Bailey transplanted baby Stephanie Fae Beuclair, performing the first xenotransplant using a baboon heart. Stephanie survived 20 days[3]. One year later, he performed the first transplant on another infant, but this time, the patient received the heart of another child. It was a successful transplant, becoming the patient with the highest survival time to date[4]. Bailey obtained excellent results in patients with left heart hypoplasia, showing that pediatric cardiac transplantation is a valid option, with results perfectly comparable to transplantation in adults[5].

According to the International Society for Heart and Lung Transplantation (ISHLT), around 100 centers worldwide report pediatric heart transplants, with more than 8,000 transplants reported between 2004 and 2014, and with an average of between 500 and 600 transplants per year[6]. Along with the increase in the number of transplants, the percentage of patients with mechanical circulatory support, used as a bridge to heart transplantation, has increased to 34.2% in 2013[6]. Thanks to the surgical technique progress, as well as selection of recipients and donors, improvement of postoperative care, immunosuppression and the use of new technologies, survival records have improved year after year[6-8].

From the aetiological point of view, transplant indications vary according to age, being those "incorrigible" congenital malformations the main indication for transplant during the first month of life. Subsequently, those diseases that primarily affect the myocardium have taken a bigger role -such as dilated or restrictive cardiomyopathies, those secondary to chemotherapy, or secondary to viral myocarditis-. In addition, in older children, adolescents and adults, some previously corrected or palliated congenital heart defects may also require another transplantation, such as patients with Fontan surgery[9].

Chile is not exempt from having these diseases. There is good coverage for congenital heart disease[10], and therefore, many children are exposed to some flaws that may improve and benefit from this therapy. It is estimated that about 10% of children born with congenital heart disease will require transplantation. In addition to this fact are cardiomyopathies, which are diseases that affect the heart muscle. In Pediatrics, they have an incidence of 1.13 cases per 100,000 and a prevalence of 2.6 cases per 100,000 children younger than 18 years old[11]. Dilated cardiomyopathies of idiopathic origin (DCM) is the most common cause and the main reason for heart transplantation in both adults and children[12,13]. Although infrequent, with an annual incidence of 0.57 cases per 100,000 children younger than 18 years old, DCM are cause of significant morbidity and mortality, with a probability of cardiac death or transplant at 1 and 5 years of 39% and 53%, respectively[14].

In 2001, we started a pediatric cardiac transplant program to meet this demand, and as a complement to our own adult cardiac transplant program, since 1987[15]. Taking into account that this is the first pediatric cardiac transplant program, an agreement with the public health system was established from the beginning, including the whole country. According to our figures, Chile would need about 15 heart transplants per year to meet its needs.

The objective of this study is to describe and to analyze the immediate and medium-term results of pediatric patients who have been evaluated and placed on the waiting list for heart transplantation in our institution.

Material and Method

The study was conducted from a retrospective analysis of the patients registry who were enrolled for pediatric cardiac transplantation, at the Clinical Hospital of the Pontificia Universidad Católica of Chile. All patients admitted to the pediatric transplant protocol between October 2001 and July 2016 were included.

Demographic variables were recorded (age, gender, weight, health insurance system, geographic origin), diagnoses at the moment of admission, severity of illness at admission and use of ventricular assist devices. We analyzed the outcome while on the waiting list, recording the mortality of those non-transplanted patients and the waiting time until transplant or death. In the transplanted patients, specific data related to transplantation, mortality, complications, immunosuppressive treatment, rejection episodes and

medium-term survival were also analyzed. An analysis of the demographics and place of origin of the donors was also studied.

The severity of illness at the time of enrollment is conventionally defined as urgent (status I) for those patients who require hospitalization, use of vasoactive drugs and/or mechanical ventricular assistance, and non-urgent (status II) for those who can wait for their transplant at home, which means that there is no need for hospitalization[16].

Our institution has an established protocol for the evaluation of the recipient patient. The general evaluation has a medical record and a very meticulous physical examination, in addition to laboratory tests, including blood count, prothrombin time, activated partial thromboproplite, biochemical profile, thyroid tests, lipid profile, cultures, serology for citmegalovirus (CMV) and immunology. Cardiovascular evaluation consists of chest x-ray, electrocardiogram, echocardiogram, holter of arrhythmias and in some cases, stress test with measurement of oxygen consumption, together with the hemodynamic study by catheterization. A multisystem evaluation with urine sediment, urea nitrogen, creatinine clearence, lung function test and neurological evaluation with computed tomography, magnetic resonance imaging and/or electroencephalogram are performed. Finally, patients and their families are evaluated by a psychologist and social worker.

Regarding the donors, they are all patients in brain death, with normal electrocardiogram, cardiac anatomy and ventricular function. If vasoactive drugs are required, they should be given in low doses. If the donor had cardiac arrest, it should have been witnessed by the attending team ideally, and with recovery of ventricular function. They should be ABO blood type compatible with the recipient, and the ratio of donor/recipient size should be 75% to 150%, regarding newborns and infants recipients, and of +/- 20% for older children and adolescents.

The indications and contraindications in roder to be admitted in the pediatric cardiac transplant waiting list are summarized in table 1.

The surgical technique is performed with a bi-caval anastomosis technique and the myocardial protection of the donor organ with Roe's cardioplegic solution[17]. This is the technique used in patients older than one year of age. For those patients younger than one year, the bi-atrial technique is preferred, avoiding the superior vena cava anastomosis, preventing a potencial higher chance of anastomotic stenosis. Standard cardiopulmonary bypass is used, with moderate hypothermia of 30 to 32 ° C.

Prior to come off cardiopulmonary by pass, an infusion of isoprenaline, in addition to epinephrine and/or milrinone, is given as regimen. In all, transesophageal echocardiogram is performed intraoperatively once the transplant is completed.

Our immunosuppression scheme consists of: 1) steroids (methylprednisolone and prednisone); 2) calcineurin inhibitors (cyclosporin or tacrolimus); and 3) bone marrow suppressants (azathioprine or mycophenolate mofetil). Immunosuppression begins

Table 1. Definitive indications, probable indications and contraindications to enter the pediatric cardiac transplant waiting list

Indications

- Definitive
  - VO2max less than 10 ml/kg/min
  - NYHA class IV
  - Multiple hospitalizations for Heart failure
  - Recurrent symptomatic ventricular arrhythmias
- Probable
  - VO2max less than 14 ml/kg/min with significant life limitations.
  - NYHA class III.
  - Recent heart failure hospitalizations

Contraindications

- Advanced irreversible disease of another system.
- Chronic or severe acute infection.
- History of neoplasic disease.
- PAH: PVR 6-8 U Wood, TPG >15 mmHg, with no response to vasodilators and inotropes.
- Psychological or socio-cultural condition that compromises the result.
- Anatomical conditions
- Severe Allosensitization

(VO2max: Maximum oxygen consumption; NYHA: New York Heart Association; PAH: Pulmonary arterial hipertension; PVR: Pulmonary vascular resistance; TPG: Transpulmonary gradient).

Table 2. Diagnostics on admission to the pediatric cardiac transplant

Diagnosis	Number of patients	Percentage
Dilated cardiomyopathy	24	80
Restrictive cardiomyopathy	4	13.3
Single ventricle	1	3.3
Uncompacted biventricular cardiomyopathy	1	3.3

in the immediate and intraoperative preoperative period (induction with mycophenolate and methylprednisolone) and the association of tacrolimus, mycophenolate and prednisone is continued. Corticosteroids are progressively decreased, with the idea of discontinue them at 6 months post transplantation, given the magnitude of adverse effects, especially on growth and metabolic type complications. The vast majority of acute rejection episodes are treated successfully with intravenous corticosteroids. In some cases it may be necessary to use anti-T cell antibodies, as in those cases with poor response to corticosteroids or hemodynamic compromise. In addition, patients with humoral rejection also have plasmapheresis; this technique is also used prophylactically in presensitized patients.

Surveillance of rejection is performed by endomyocardial biopsy weekly the first month, bi-weekly the second month, monthly between 3-6 months and then every 3 months if there has been no evidence of rejection. After the first year the biopsies are annual, except if there are suspicious episodes of rejection, in which case the biopsies are performed as necessary for an adequate follow-up and management.

Variables are expressed in averages, medians and ranges according to distribution. An alpha value of 5% was established. Survival analysis was performed using the Kaplan-Meier method. Statistical analysis was performed using the IBM SPSS Statistics v20.0 statistical package.

The present study does not have conflicts of interest and has the approval of the Research Ethics Committee of the Clinical Hospital of the Pontifica Universidad Catolica de Chile

Results

The series has 30 patients, 17 males (56.7%) and 13 females (43.3%), with a mean age of 9.4 years (1 month to 15 years) and an average weight of 33.6 kg (4 to 57 kg). Regarding their health insurance coverage, 19 patients were beneficiaries of FONASA (public insurance) (63.3%) and 11 patients were beneficiaries of ISAPRE (private insurance) (36.7%). 56.7% come from places outside the Metropolitan Region (17 patients).

The main diagnosis was dilated cardiomyopathy in 80% of the cases (24 patients). Restrictive cardiomyopathy was present in 4 patients (13.3%), one of whom was secondary to chemotherapy due to a cardiac rhabdomyosarcoma. Only one patient had a single ventricle congenital heart disease (3.3%) and one case had uncompressed cardiomyopathy (3.3%) (table 2).

The severity of illness at the moment of entry to the waitng list was urgent (status I) in 63.3% of cases (19 patients) versus non-urgent (status II) in 36.7% (11 patients).

Among all patients enrolled, 14 were transplanted (46.67%) and 10 patients died waiting for the transplant (33.3%). A 1-year-old patient diagnosed with dilated cardiomyopathy was removed from the waiting list because of clinical improvement. Currently 5 patients are on the waiting list.

In the outcome of those 10 non-transplanted patients, the time from listing until death was a mean of 52 days (13 to 139 days), with mean age of admission of 8 years and 2 months (2 years 5 months to 15 years) and mean weight of 22 kg (12 to 49 kg). All patients died due to progression of heart failure or complications associated with mechanical ventricular support, as described below.

Although there was a higher proportion of patients in status I among those who died waiting for transplantation (90.9%) compared to the number of patients in status I who were able to get transplanted (57.14%), this difference did not reach statistical significance ($p = 0.067$).

Fourteen patients (46.7%) were transplanted, with a mean age of 11.4 years (3.3 to 14.8 years), mean weight of 43 kg (14 to 93 kg) and an mean waiting time of 199.6 days (4 to 586 days). Surgical technique was performed with bi-caval technique in all patients, with an average ischemia time of 146 min (± 50.6 min) and hospitalization time of 26.7 days (± 16.35 days). The results are summarized in table 3. The surgical technique is illustrated in figure 2.

The mean post-transplant follow-up was 43 months (0.5 to 159 months). Operative mortality was 7.14%, corresponding to a 10-year-old patient, who died at 16 days due to primary failure of the graft plus a fungal infection. This patient required postoperative ventricular assistance with Extracorporeal Membrane oxygenation (ECMO), being the only case requiring post-transplant circulatory support.

All transplanted patients received tri-associated immunosuppressive therapy according to the established protocol. Eight patients (57.14%) presented at

least one acute rejection episode, of which 5 presented cellular rejection (35.7%) and 2 patients presented humoral rejection (14.28%). There was one patient who presented both types of rejection (7.14%).

Two patients died (14.28%), at 55 and 82 months respectively, both due to acute rejection associated with the abandonment of the immunosuppressive treatment. Survival at one year was 93% and at 5 years 74%, as shown in figure 1. Overall 5-year survival for the total cohort of patients enrolled was 43.1% (figure 1).

Other immediate or late complications following transplantation were CMV infection (4 patients), Mycoplasma infection (2 patients), steroid diabetes (2 patients), swallowing disorder (2 patients), stroke (1 patient), venous thrombosis (1 patient), pulmonary thromboembolism (1 patient), atrial flutter (1 patient), and Hodgkin's lymphoma (1 patient).

The geographic place of origin of the donor organs were: 2 from the IV th region, 9 from the Metropolitan Region, and from regions VII th, VIII th and IX th, one of each, being Coquimbo, by the north and Temuco, by the south, the most distant places. The mean age of donors was 23.9 years (2 to 45 years), with a mean weight of 51.7 kg (12.5 to 65 kg).

Among all 30 patients, 9 required mechanical ven-

Table 3. Characteristics of the 14 transplanted patients

Feature	n = 14
Age, average (range)	11.4 years (3.3 a 14.8 years)
Weight, average (range)	43 kg (14 a 93 kg)
Status I, percentage	50%
Waiting time, average (range)	199.6 days (4 a 586 days)
Isquemia time, average (range)	146 minutes (± 50.6 min)
Hospitalization time, average (range)	26.7 días (± 16.35 days)
Cellular rejection, number of cases (percentage)	5 (35.7%)
Humoral rejection, number of cases (percentage)	2 (14.28%)
Cellular & Humoral rejection, number of cases (percentage)	1 (7.14%)

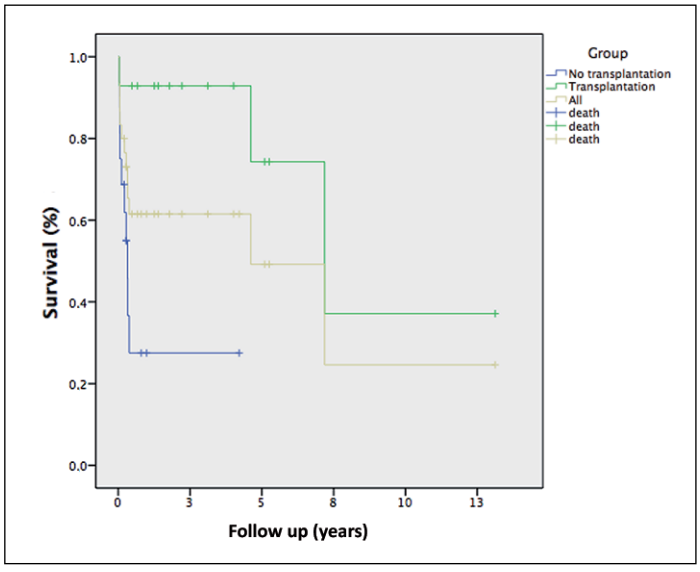

Figure 1. Survival rates in transplanted, not transplanted and overall patients.

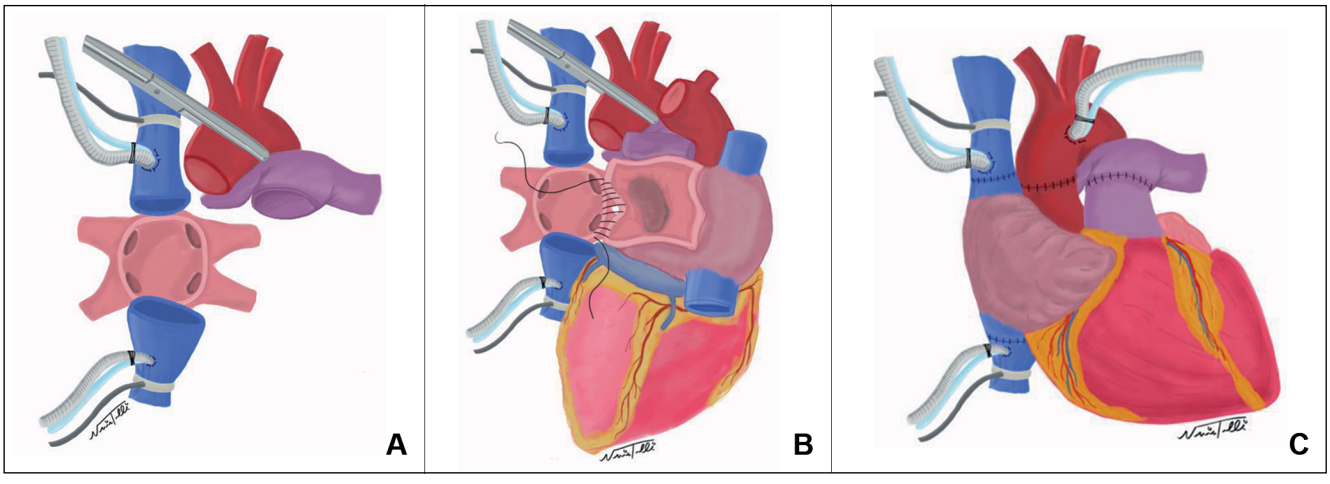

Figure 2. A. Explanted recipient heart showing left atrial remnant with 4 pulmonary veins, ascending aorta, distal trunk of pulmonary artery, superior and inferior vena cava. **B.** Heart transplantation. Initiation of anastomosis between the left atrium of the donor heart and left atrial remnant of the recipient. **C.** Complete cardiac transplantation showing the 5 anastomosis sequentially constructed in the following order: left atrium, inferior vena cava, pulmonary artery trunk, ascending aorta and superior vena cava.

tricular assistance (30%) as bridge to transplantation. The different devices utilized were : 1 Bio Medicus, 2 ECMO, 2 Berlin Heart Excor, 3 Centrimag Levitronix and 1 Heart Ware (figure 3).

Of these 9, 4 were transplanted, 4 died and 1 is currently on the waiting list. Of the deceased patients, one was connected to a bi-ventricular assist with a Bio Medicus pump, who died due to multi organ failure, with prolonged ventricular assistance. The second was a patient connected to ECMO in extreme conditions who

Table 4. Features of patients and respective donor

	Patient	Donor		Patient	Donor
1	Male 10 years 0 IV PRA 6% CMV (+) HLA AB: A1, A2, B35, B39 HLA DR: DR16(2), DR11(5)	Male 3 years 10 meses 0 IV CMV (+)	8	Female 12 years 0 IV PRA 0% CMV (+) HLA AB: A24, A29, B39, B44 HLA DR: DRB1*07, DRB1*09	Female 43 years 0 IV CMV (+)
2	Male 9 years A II PRA 15% CMV (-) HLAAB: A02, A68(28), B35, B39(16) HLA DR: DR 04 (DR53)	Male 11 years All CMV (+)	9	Female 13 years 0 IV PRA 0% CMV (+) HLA AB: A01, A68, B35, B51 HLA DR: DRB1*08, DRB1*14	Female 30 years 0 IV CMV (+)
3	Male 10 years 0 IV PRA - - CMV (-) HLA AB: A3, A32, B35, B51 HLA DR: DRB1*4, DRB1*11	Female 9 years 0 IV CMV (+)	10	Male 3 years 4 meses A II PRA 0% CMV (+) HLA AB: A01, A02, B08, B44 HLA DR: DRB1*04, DR 53	Female 2 years 9 meses 0 IV CMV (+)
4	Female 11 years A II PRA 0% CMV (+) HLA AB: A24, B37, B39 HLA DR: DRB1*04, DRB1*13	Male 16 years 0 IV CMV (+)	11	Male 14 years AH PRA 7% CMV (+) HLA AB: A11, A68, B07, B40 HLA DR: DRB1*09, DRB1*15	Female 39 years A II CMV (+)
5	Female 13 years 0 IV PRA 3% CMV (+) HLA AB: A01, A02, B08, B51 HLA DR: DRB1*03, DRB1*04	Female 26 years 0 IV CMV (+)	12	Male 12 years 0 IV PRA 0% CMV (+) HLA AB: A01, A68, B35, B37 HLA DR: DRB1*13, DRB1*16	Male 26 years 0 II CMV (+)
6	Male 13 years 0 IV PRA 0% CMV (+) HLA AB: A11, A80, B15, B51 HLA DR: DRB1*07, DRB1*15	Female 22 years 0 IV CMV (+)	13	Male 14 years A II PRA 0% CMV (-) HLA AB: A02, A32, B14, B51 HLA DR: DRB1*07, DRB1*13	Male 26 years 0 IV CMV (+)
7	Male 13 years 0 IV PRA 10% CMV (-) HLA AB: A32, A68, B39, B49 HLA DR: DRB1*04, DRB1*14	Female 45 years 0 IV CMV (+)	14	Male 14 years 0 IV PRA 3% CMV (+) HLA AB: A29, A33, B51, B14 HLA DR: DRB1*01, DRB1*11	Male 23 years 0 IV CMV (+)

(CMV: Citomegalovirus, HLA: Human leukocyte antigen, PRA: Panel reactive antibody).

could not recover from multi organ failure as well, not being a candidate to escalate to ventricular assistance. The third deceased, was connected to biventricular assistance with the Berlin Heart Excor system, developed severe hemorrhage from the upper digestive apparatus associated with blood bronchoaspiration; the fourth deceased, also with biventricular assistance with Berlin Heart Excor, had a mechanical malfunction of the right pump, which caused secondarily cerebral infarction due to several minutes of low output, with subsequent hemorrhagic transformation and brain death.

Discussion

Pediatric cardiac transplantation accounts for about 10% of total heart transplants in the world (18). There are some peculiarities that make this treatment quite unique compared to the transplant in adults: there are anatomical variants resulting from congenital malformations that can make the transplant technically more challenging; There are limitations on the size of potential donors, especially in young children; There may be variations in the degree of maturity of the immune system; greater possibility of requiring a new transplant and the existence of special needs from a psychosocial point of view, among others. For these reasons, a specially trained and dedicated team is required, as is conventional pediatric cardiac surgery compared to adult cardiac surgery[19].

The predominant diagnosis in our patients was cardiomyopathy and within them the dilated type (80%). This is in part in agreement with the International Society for Heart and Lung Transplantation, in which, in the age group between 1 and 10 years of age, cardiac muscle alterations represent 55%, against 36% of congenital malformations, and in the group above 11 years, cardiomyopathies represent 64%[6]. The significant prevalence of cardiomyopathies in relation to congenital malformations in our series can be explained by the fact that within this second group, patients are usually more severily ill and therefore can not be referred to in a timely manner. Another explanation for this may be related to the lack of knowledge of the national medical community about the possibility of transplantation as an alternative treatment for incorrigible congenital heart disease and are not referred for a timely evaluation. Although Chile has good coverage of congenital heart disease and most of them are opportunely corrected or palliated, those that may require transplantation are usually more sick and occur within the first or second year of life, a period in which obtaining donors is particularly difficult in our environment. In our group we considered transplantation as an option in patients with univentricular pathology

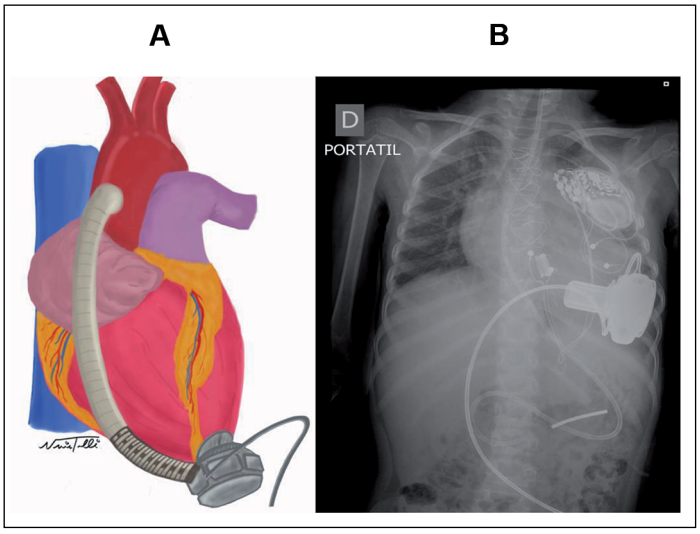

Figure 3. Diagram of Heart Ware ventricular assist device **(A)** and chest X-ray control of a 7-year-old patient with device installed **(B)**.

who are not suitable candidates to complete a staging until a Fontan surgery, but being in practice very difficult to perform transplants at very early ages.

When enrolling patients for transplantation, a high proportion did so in an emergency basis or status (63.3%), which is comparable to other multicentric series and registries[8,20,21]. However, the mortality of 33.3% in our program is higher than that reported in these series, in which mortality has been observed between 20 and 27% for patients enrolled in status I and less than 10% for those enrolled in status II. This higher mortality could be explained by the lower use of ventricular assist devices in the early era of our experience and by a greater difficulty in obtaining donors in our environment.

The use of mechanical circulatory support has contributed to decrease mortality on the waiting list, as demonstrated by the multicenter study by Blume et al. in which the mortality at 6 months post listing decreased from 25% to 7%, with an mean waiting time until transplant of 57days[22]. We incorporated mechanical ventricular support more routinely during the second half of our experience, as the availability and access to these devices improved. Thirty percent of our patients required mechanical ventricular support, with survival to the transplant of 44.4% and mean waiting time of 62.7 days. The available devices are still far from being free of complications, specially if the required time of ventricular assistance until transplantation extends too long. The most used and tested system in paediatrics is the Berlin Heart Excor System, used in 2 patients in our experience[23]. Its main advantage is the versatility, since it can be used for uni or bi-ventricular assistance

and from small infants to adults; The main disadvantages are the high levels of anticoagulation required, being paracorporeal and that in pediatric patients requires that they stay hospitalized. Recently there has been a greater use of continuous flow devices and implantable in pediatric patients (as opposed to the pulsatile systems, such as the Berlin Heart, which is also paracorporeal). Although these correspond to systems designed for adults, such as Heart Mate II and Heart Ware, they have been successfully used in some children, mainly those with a body surface less than 1.5 m^2, where the Heart Ware system is smaller and was used in one case in our series. One of the main advantages of this type of devices is that patients can eventually be discharged and wait for the transplant outside the hospital. In experiences such as that of Mathew et al.[24], patients with ventricular assist were transplanted within 37 days, compared to 62 days in our experience.

In the transplant group of patients, there was operative mortality in one (7.14%) due to graft failure, who required postoperative ECMO, complicated by fungal sepsis. This mortality of less than 10% compares favorably with other series, as well as the frequency and type of complications[25-27].

Regarding immunosuppression, it has undergone some changes over time. The goal is to prevent and treat rejection of the transplanted organ, along with minimizing the toxic effects and major complications of immunosuppressive drugs, namely, infections and cancer. Most immunosuppressive regimens include a combination of various drugs, thereby achieving greater effectiveness, as there are different mechanisms, sites of action and a synergistic action with less toxicity of the individual agents. An important principle of immunosuppression is that the immunological reactivity and the tendency to exist rejection is high in the first 3 to 6 months post-transplantation and then decreases progressively with time, which is why most of the schemes employ a high intensity of immunosuppression immediately post surgery. Subsequently, low levels of immunosuppression are established to avoid rejection and decrease the likelihood of associated toxicity. Drugs that inhibit T cell activation (calcineurin inhibitors) are the basis of immunosuppressive therapy; In recent years we have preferred the use of tacrolimus over ciclosporin, given the lower toxicity of the former, especially gingival hyperplasia and hirsutism[28]. We have also replaced the use of azathioprine with mycophenolate, since it has a more selective action on the proliferation of T lymphocytes at the medullary level[29].

Long-term follow-up of our 14 transplant patients showed a 74% survival at 5 years, similar to that reported by other series[25-27,30]. The cause of death was the abandonment of immunosuppressive treatment in the two patients who died during follow-up. This is a warning sign about the importance of these children and adolescents having an adequate support network. Psychosocial evaluation of the child and his/her parents is a fundamental part of the decision to enroll a patient. Although they are not part of this study because they were not listed, we have discarded two patients for serious reasons of this nature.

The program has managed to transplant about 50% of patients enrolled, with a significant mortality rate on the waiting list (33%). Those transplanted patients had an average waiting time of approximately 200 days, ranging from 14 to 586 days, evidencing that the availability of pediatric organs is a serious limiting factor. Unlike adults, children have a universe of potential donors that is smaller, since there must be some concordance of weight and size between recipient and donor, as was described in the methodology of our protocol. This is also particularly complex in children who are candidates for heart transplantation, compared to children who require transplantation of other organs, such as liver or kidney; where in these cases adult donation can be received, being feasible to house an adult kidney in the abdomen of a child, as well as implant a lobe or segment of the liver of an adult in a pediatric patient. This possibility does not exist in the case of the heart, which must be housed entirely within the thoracic cavity, with less chance to accommodate a larger organ and having to function with a certain pre and after-load.

The success of a national pediatric cardiac transplant program depends critically on the technical quality and expertise of the entire health team involved, the progress of immunosuppression, and the technology to provide safe ventricular assistance to a growing number of patients . However, pediatric cardiac transplantation is strongly conditioned to the timely collection of donors as one of the major limiting factors. Even the connection to ventricular assistance as a bridge to transplantation must be associated with the feasibility of obtaining an adequate donor within a short period of time, which is still very difficult in Chile.

Improvements in donor policy and optimization of available resources are undoubtedly needed to increase the research and adequate search of potential pediatric donors. At present time it is practically a theoretical exercise to put a child under 3 or 4 years of age on the waiting list, especially if it is an urgency (status I), because there are few potential donors compatible with young patients. Even the use of ventricular assist at these ages involves a long waiting period, with the potential complications inherent to these advanced and complex therapies. The youngest patient in our series was 3 years old but managed to wait for a donor at home for 11 months (status II), so it may be realistic

to list, for now, only non-urgent patients in this age group, which has been our practice in general.

The ways to reverse this situation are to improve our population's education regarding organ donation, specifically to contribute to a better understanding of what brain death means in terms of its irreversibility and to demonstrate the transparency of the organ allocation system. Alongside this, it is essential to provide more pediatric intensive care units with technical and human resources to identify donors, provide them with appropriate care, and enable donation and organ procurement.

Conclusion

Pediatric cardiac transplantation, analyzed as an isolated procedure, is an effective and safe therapy in our setting, with good survival in the medium term. However, this is limited by a significant mortality on the waiting list, so this therapy, viewed globally, has limited effectiveness. The main limiting factor is timely donor procurement. An increase in the rate of effective donors along with the development of better mechanical ventricular assist devices, designed especially for children, can contribute to improve this scenario.

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author.

Conflicts of Interest

Authors state that any conflict of interest exists regards the present study.

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