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Pediatric and congenital heart transplant: twenty-year experience in a tertiary Brazilian Hospital

Experiência de 20 anos com transplante cardíaco pediátrico e em portadores de cardiopatias congênitas

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Abstract

Introduction: **Cardiac transplantation remains the gold standard for end-stage cardiomyopathies and congenital heart defects in pediatric patients.**

Objective: **This study aims to report on 20 years of experience since the first case and evaluate our results.**

Methods: **We conducted a retrospective analysis of the database and outpatient follow-up. Between October 1992 and April 2012, 109 patients underwent 114 transplants. 51.8% of them being female. The age of patients ranged from 12 days to 21 years with a mean of 8.8±5.7 years and a median of 5.2 years. The underlying diagnosis was dilated cardiomyopathy in 61.5%, congenital heart disease in 26.6% and restrictive cardiomyopathy in 11.9%. All patients above 17 years old had congenital heart disease.**

Results: **Survival rate at 30 days, 1, 5, 10, 15, and 20 years were 90.4%, 81.3%, 70.9%, 60.5%, 44.4% and 26.7%, respectively. Mean cold ischemic time was 187.9 minutes and it did not correlate with mortality (*P*>0.05). Infectious complications and rejection episodes were the most common complications (*P*<0.0001), occurring, respectively, in 66% and 57.4% of the survivors after 10 years. There was no incidence of graft vascular disease and lymphoproliferative disease at year one, but they affected, respectively, 7.4% and 11% of patients within 10 years.**

Conclusion: **Twenty-year pediatric heart transplant results at our institution were quite satisfactory and complication rates were acceptable.**

Descriptors: **Heart Transplantation. Heart Defects, Congenital. Cardiomyopathies. Tissue Donors. Donor Selection. Graft Rejection. Cold Ischemia.**

Resumo

Introdução: **O transplante cardíaco tem sido o tratamento de escolha para pacientes pediátricos portadores de miocardiopatias e portadores de cardiopatias congênitas em fase final da doença.**

Objetivo: **Relatar a experiência de 20 anos do serviço e avaliar seus resultados.**

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Abbreviations, acronyms & symbols	
GVD	Graft vascular disease
HTx	Heart transplantation
NYHA	New York Heart Association

Métodos: **Estudo retrospectivo por meio de análise do banco de dados. Entre outubro de 1992 e abril de 2012, 109 pacientes foram submetidos a 114 transplantes. 51,8% eram do sexo feminino. A idade dos pacientes variou de 12 dias a 21 anos, com média de 8,8±5,7 anos e mediana de 5,2 anos. O diagnóstico de base dos pacientes foi de miocardiopatia dilatada em 61,5%, cardiopatias congênitas em 26,6% e miocardiopatia restritiva em 11,9%. Todos os pacientes entre 17 e 21 anos eram portadores de cardiopatias congênitas.**

Resultados: **A sobrevida em 30 dias, 1, 5, 10, 15 e 20 anos foi de 90,4%, 81,3%, 70,9%, 60,5%, 44,4 e 26,7%, respectivamente. O tempo médio de isquemia do órgão transplantado foi de 187,9 minutos e não teve correlação com a mortalidade (*P*>0,05). Intercorrências infecciosas e rejeição foram as complicações mais incidentes (*P*<0,0001), atingindo 66 e 57,4% dos sobreviventes após 10 anos. A incidência de doença vascular do enxerto e doença linfoproliferativa foi zero no primeiro ano e atingiu, respectivamente, 7,4 e 11% dos pacientes em 10 anos.**

Conclusão: **O Transplante Cardíaco neste grupo de pacientes pediátricos e portadores de cardiopatias congênitas pôde oferecer resultados satisfatórios, com uma taxa de complicações aceitável ao longo do seguimento.**

Descritores: **Transplante de Coração. Cardiopatias Congênitas. Cardiomiopatias. Doadores de Tecidos. Seleção do Doador. Rejeição de Enxerto. Isquemia Fria.**

INTRODUCTION

Despite recent advances in stem cells research and breakthroughs in the diagnosis and clinical management of heart failure (HF), heart transplantation (HTx) is still considered the best therapeutic strategy to increase survival and improve symptoms in end-stage HF patients[1].

In children, the occurrence of conventionally untreatable congenital heart disease and severe cardiomyopathy may be indications for this procedure. However, HTx in the pediatric population still faces greater difficulties than in adults due to greater scarcity of donors or technical difficulties imposed by some congenital malformations[2].

Recently, Jacobs et al.[2] reported their experience with just over 100 pediatric HTx and found that the presence of congenital heart disease did not increase mortality compared with cardiomyopathies. However, heterotaxy and reoperations in patients with congenital heart disease, decrease the chances of survival.

In Brazil, the first HTx in a newborn was performed at our institution in November 1992[3]. In April 2012, our team of Pediatric and Congenital Heart Surgery held its hundredth HTx, consolidating its position as the largest and most active center outside Europe and North America[4].

We have several publications in this area, from 1996, when we published our initial experience[3,5-8], to our two most recent studies, one addressing the results of HTx in patients with cardiogenic shock[9] and another in patients with rejection and cyclosporine intolerance[10].

At the moment, a reflection on these 20 years of experience is important for the cardiology and cardiac surgery communities, especially in Brazil, to show our current status and which aspects are in need to more attention and improvement.

Objective

This study aims to report our experience and evaluate our results.

METHODS

This study was conducted hrough retrospective analysis of our database after approval by the Ethics in Research Committee of our institution. Regarding infections, the database of the Committee on Infection Control was used.

Patients

Between October 1992 and April 2012, 109 pediatric and congenital heart patients underwent 114 HTx, with five re-transplants. The age of patients ranged from 12 days to 21 years (mean=8.8±5.7 years, median 5.2 years). Among the 109 patients, 11 were between zero and one year of life (10.1%), 71 were between one and 10 years-old (65.1%), and 27 were older than 10 at the time of operation (24.8%). Two patients above 17 years old with congenital heart disease were included in this sample. The distribution of patients according to age and diagnosis is shown in Figure 1.

Primary diagnosis varied from cardiomyopathy in 80 patients (73.4%) and congenital heart disease in 29 (26.6%). Among those with congenital heart disease, 10 patients had single-ventricle physiology (Table 1), 23 (79.3%) had undergone to previous surgery prior to HTx hospitalization, one (3.5%) patient with Ebstein's anomaly had undergone surgical correction and developed acute ventricular dysfunction being subjected to urgent HTx after circulatory support. Five had not been submitted to any previous surgical procedure (17.2%).

Donor age ranged from 8 months to 52 years (mean = 13.8±10.5 years, median=11 years). The average weight of donors was 39.8±23 kg, while recipient mean body weight was 20±13.9 kg. The average weight mismatch between donor and recipient was 2.1±0.7. Gender distribution was mostly homogeneous (51.8% female).

The number of HTx per year ranged between 1 and 18 procedures (average=6 HTx/per year). There has been an upward trend in the number of cases in recent years. Follow-up was conducted through personal contact during out-patient consultations and/or consultation using the electronic medical record or phone calls.

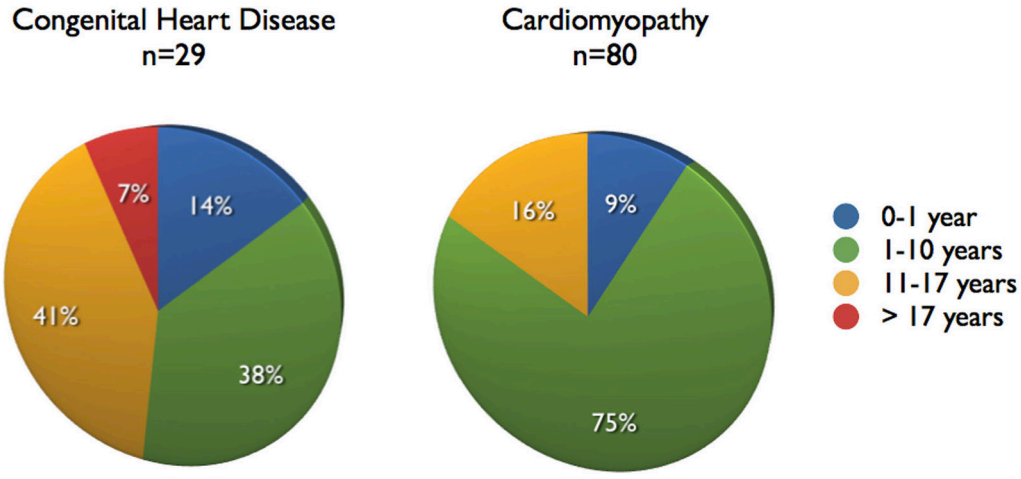

Fig. 1 - Age distribution between congenital heart disease and cardiomyopathy.

Table 1. Diagnosis and previous surgical approach in patients with congenital heart disease.

Diagnosis	Previous surgical approach	N
AV block + pacemaker	yes	4
DORV	yes	4
Ebstein's anomaly	yes	3
HLHS	no	2
PA IVS	yes	2
TA	yes	2
Single ventricle	yes	2
CCTGA	yes	2
VSD	yes	1
Uhl's Anomaly	no	1
Mitral insufficiency + AV block	yes	1
Truncus arteriosus	yes	1
Tetralogy of Fallot	yes	1
ASD + restrictive cardiomyopathy	no	1
TGA + Senning	yes	1
IAS aneurysm and mitral valve prolapse	no	1
Total		29

Surgical technique

The surgical technique employed involved bicaval and aortic cannulation for extracorporeal circulation with moderate hypothermia (30ºC). Bicaval anastomosis was performed in most cases. When hypoplastic left heart was present, innominate artery cannulation was performed and periods of deep hypothermic selective cerebral perfusion for aortic arch reconstruction were used.

When there was previous surgery involving the pulmonary arteries (PA's), as in Glenn or Fontan operations, it was necessary to carry out reconstruction of the PA's through different techniques. The presence of persistent left superior vena cava demanded that it be connected with the right superior vena cava using a graft or the donor innominate vein itself.

Myocardial protection was achieved by using cold crystalloid antegrade Roe's solution[11], at the time of organ harvesting. This formula has been used since the first procedure in 1992 until the present day. When the predicted ischemic time was longer than three hours, it was decided to repeat cardioplegia before beginning the anastomosis.

Immunosuppression protocol

The immunosuppression protocol for patients who have negative prospective crossmatch is based on continuous infusion of perioperative cyclosporine (infusion starts 6 hours before implant), corticosteroids associated with human immunoglobulin and rabbit antithymocyte globulin. For those with positive prospective crossmatch, plasmapheresis was also performed, 5 sessions on alternate days, in addition to other cytolytic and immunosuppressive drugs and the immunomodulators already mentioned[12].

Statistical analysis

Descriptive data were presented in mean ± standard deviation. To evaluate the survival of pediatric heart transplant in 20 years the actuarial survival Kaplan Meier method was used. To assess the impact of diagnosis and age on survival, the Cox proportional regression was used. The statistical software program used was the Statistical Package for Social Sciences for Windows, v. 11.5 (SPSS Inc, Chicago, IL). It was adopted as significant a *P*-value of less than 0.05.

RESULTS

Survival

The 30-day survival was 90.4%. Survival at one, five, ten, fifteen and twenty years was 81.3%, 70.9%, 60.5%, 44.4% and

26.7%, respectively (Figure 2). Mean follow-up was 8 years. Median survival of patients after HTx was 11.07 years (9.33 to 12.8, CI 95%) and the median was 11.57 years (7.72 to 15.42, CI 95%).

The Cox proportional regression analysis of the impact of age on survival revealed no statistical significance (*P*=0.198). In the same manner, the diagnosis of congenital heart disease was not a predictor of poor survival during follow-up (*P*=0.126). Survival curves of patients with congenital heart disease and cardiomyopathies are shown in Figure 3.

Complications

Infectious complications and rejection episodes were the most common complications during follow-up. We observed an average of three rejection episodes per patient over the 20 years of follow-up. As it can be seen in Figure 4, after 20 years of follow-up, almost all patients had at least one episode of infection and/or rejection. There was a statistically significant difference (*P*<0.0001) compared to the incidence of other complications, such as graft vascular disease (GVD) and lymphoproliferative disease.

There was no occurrence of GVD and lymphoproliferative disease in the first two years after HTx. However, after 15 years of follow up, there was an incidence of 7.4% and 20.2%, respectively. Of the patients affected by GVD, two of them underwent stent implantation in the affected coronary artery. One showed good results; however, coronary artery bypass grafting was indicated in the second case due to persistent myocardial ischemia. Another two of the GVD patients underwent re-transplantation and the other two are currently listed.

Lymphoproliferative disease affected eight patients over the 20-year follow-up. Three had pulmonary lesions, two had abdominal location, and three had polyadenopathy. Four patients (50%) died, and the deaths of two of them were related to lymphoproliferative disease. The remaining four patients had disease regression and show good progress. Figure 4 shows the curves of incidence of major complications.

Five patients had undergone re-transplantation, two due to GVD and three because of graft rejection.

Causes of death

The causes of mortality varied over time and data are detailed in Table 2.

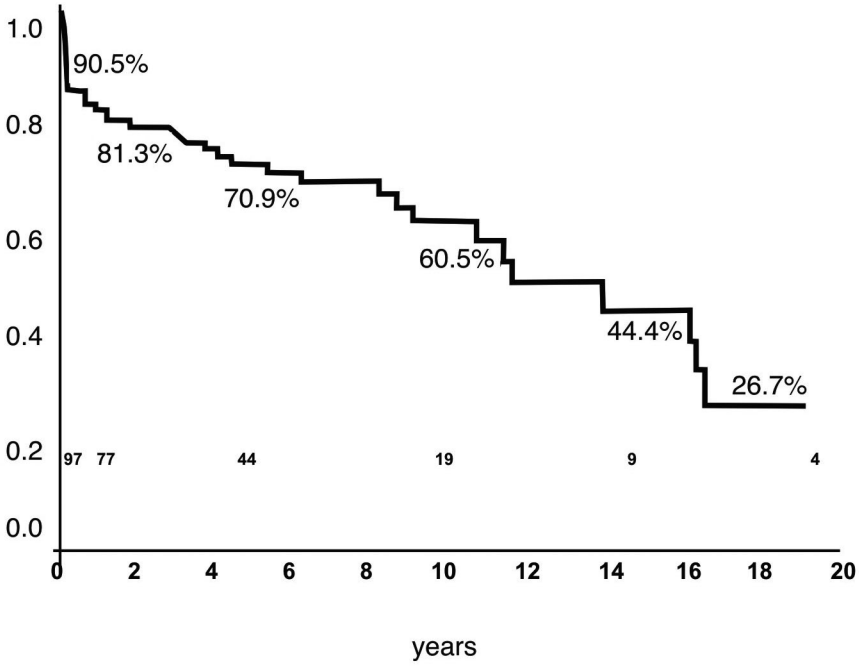

Fig. 2 - Actuarial Survival graph including all patients submitted to heart transplant. 30-day survival=90.5%; 1 year=81.3%; 5 years=70.9%; 10 years=60.5%; 15 years=44.4%; 20 years=26.7%; patients at risk: time zero=109, 30 days= 97, 1 year=77, 5 years=44, 10 years=19, 15 years=9, 20 years=4

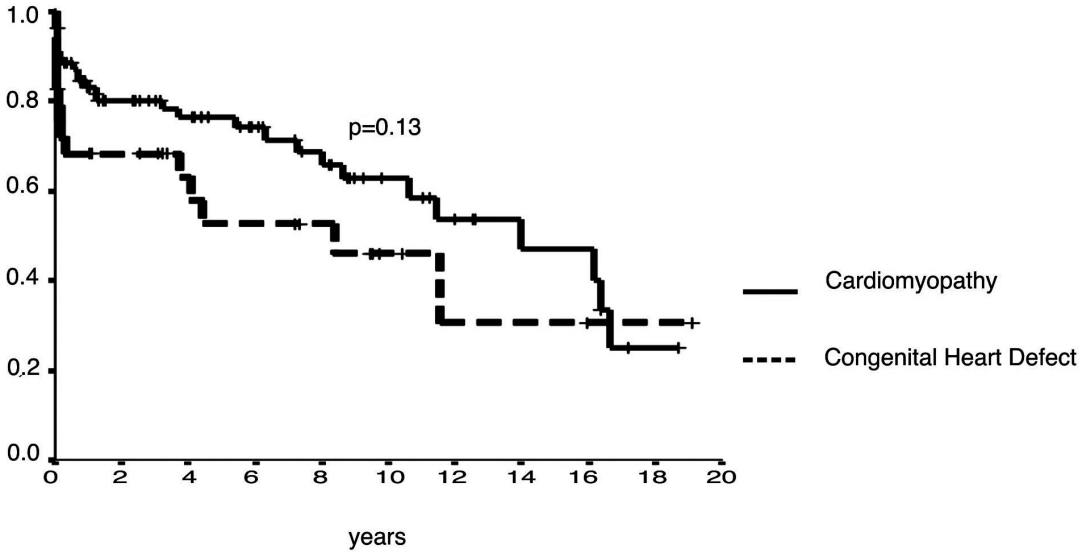

Fig. 3 - Comparative graph between survival with Congenital Heart and Cardiomyopathy after Heart Transplant. P=0.13 with Cox proportional regression analysis.

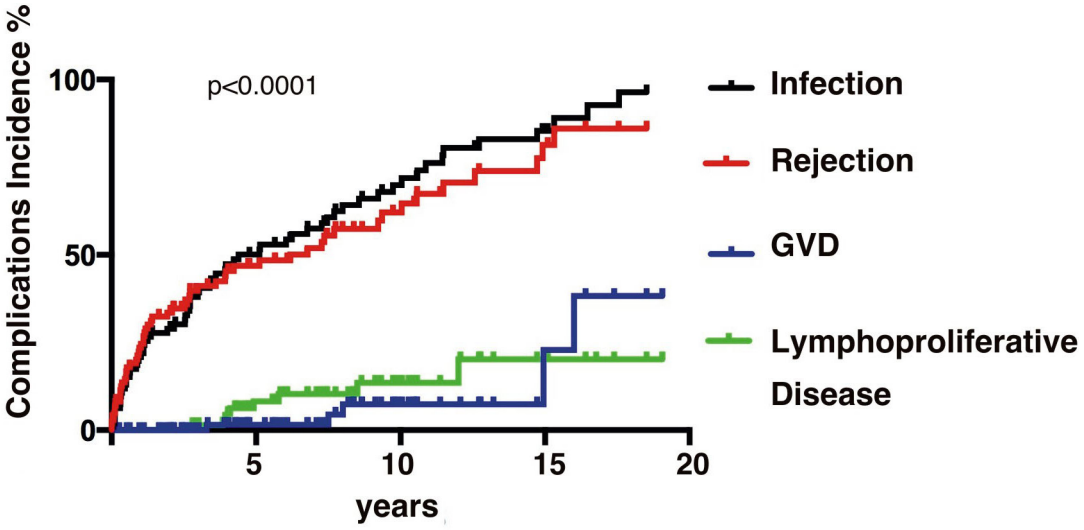

Fig. 4 - Graph illustrating incidence of complications during Heart Transplant follow-up.
GVD= Graft Vascular Disease; n= number of patients at risk
P>0.05 when comparing infection versus rejection; P<0.0001 when compared Infection versus GVD; P<0.0001 when comparing infection versus Lymphoproliferative Disease; P<0.0001 when comparing rejection versus GVD; P<0.0001 when comparing rejection versus Lymphoproliferative Disease; P>0.05 when comparing GVD versus Lymphoproliferative Disease

Table 2. Causes of death according to the time of HTx follow-up.

Time of Follow-up	MODS (%)	Rejection (%)	Infection (%)	Sudden Death (%)	GVD (%)	Lynphoproliferative Disease (%)	Primary Graft Disfunction (%)	PTE (%)
0-30 d	1(16.6)	6(60)	1(10)	-	-	-	2(100)	
30 d-1 y	4(66.8)	3(30)	5(50)	1(16.7)	-	-		
1 y -5 y	-	-	1(10)	2(33.3)	1(33.4)	1(50)		
5y-10 y	-	-	1(10)	3(50)	-	-		1(100)
>10 y	1(16.6)	1(10)	2(20)		2(66.6)	1(50)		
Total (%)	6(15)	10(25)	10(25)	6(15)	3(7.5)	2(5)	2(5)	1(2.5)

d=days; y=years; MOD=Multiple organ disfunction; GVD=graft vascular disease; PTE=pulmonary thromboembolism

Cold ischemic time

Mean organ's cold ischemic time was 187.9±72.3 minutes. Cold ischemic time was less than 60 minutes in 10 cases (8.8%), between 61 and 120 minutes in 31.6% of the cases (36 cases), 121 to 180 minutes in 25.4% (29 patients), 181 to 240 minutes in 17 (14.9%), 241 to 300 minutes in 16 cases (14%) and above 301 minutes in 5.3% of cases (6 HTx). However, in this study, the ischemic time had no direct correlation with mortality (*P*=0.23).

Geographical origin of receivers and donors

The geographical origin of receptors in Brazil was very diverse, covering 18 states and the Federal District. Nevertheless, the uptake of organs occurred almost entirely in the state of São Paulo, with 93% of the cases. The rest (7%) of the donors were located in other states, namely: Santa Catarina, Rio de Janeiro, Minas Gerais, Goiás, and the Federal District.

There was an offer of 621 organs in these 20 years, 68% from individuals aged 16-20 years (422 donors), 17% aged 11-15 years (106 donors), 8% aged 6-11 years (50 donors), and 7% aged 0-5 years (43 donors). However, most potential donors were rejected due to weight mismatch or hemodynamic instability.

Circulatory support

The use of circulatory support in this series was observed in only three patients in whom extracorporeal membrane oxygenation (ECMO) was used. These patients were in severe cardiogenic shock. Hospital discharge was possible for one of them after transplantation. Multiple organ failure was the cause of death of the other two.

DISCUSSION

The first pediatric heart transplant was performed in Brazil more than 20 years ago, and it was only possible thanks to a two-year preparation based in Loma Linda protocols. This preparation was made through an important expertise transfer, accompanied by visits from our team to the Californian hospital. Loma Linda was the birthplace of pediatric HTx, since the enormous contributions of Bailey et al.[13] who transplanted a baboon heart in small Fae, stricken with hypoplastic left heart syndrome, who later became known worldwide as baby Fae.

Extracorporeal circulation and myocardial protection

Despite the constant development of cardiovascular surgery, few changes have occurred in our protocol over the twenty years. Myocardial protection remains identical and has been working well, since we observed less than 2% of deaths related to primary graft dysfunction, despite an often extended cold ischemic time. Extracorporeal circulation has evolved considerably in the interim, accompanied by HTx, with the incorporation of monitoring line pressures and association of modified ultrafiltration for patients below 30 kg. The protocol of moderate hypothermia has been kept.

Cold ischemic time

In our series, cold ischemic time was on average three hours and it did not correlate with mortality. The influence of ischemic time in post-HTx mortality finds considerable controversy in the literature. While some authors corroborate our findings[14], others believe that ischemic time is an independent predictor of mortality after HTx[2]. Even with our policy of preference for uptake within the state itself (93% of the time), in 19% of the cases, the ischemic time was longer than 4 hours. Longer ischemic times were caused mostly by logistical problems in transportation, since it is a big state and mobility some times may be difficult, and technical difficulties related to the implant, such as in re-operations and anatomical challenges related to congenital hearts, with the need to reconstruct the venous drainage and/or the pulmonary arteries.

Re-transplantation

A recent North American study in pediatric HTx with more than 4000 cases attributed increased mortality to re-transplantation[15], although Jacobs et al.[2] and Kanter et al.[14] have shown to be possible to obtain results superimposed to the first intervention. We had a low incidence of re-transplantation (4.4%); however, the survival of these

patients did not differ from patients undergoing primary Tx, corroborating these authors[2,12].

Circulatory Support

The outcome of patients not listed as priority in our institution was similar to that reported recently by North American researchers, who analyzed the outcome of pediatric patients listed for HTx[15].

However, our mortality rate in the priority list was high, as we already demonstrated in 2008, when we studied patients with cardiogenic shock[9]. This is due to the obvious severity of the disease and donor shortage for pediatric patients, especially, when HTx needs to be performed on an emergency basis.

The use of circulatory support could help reduce mortality in this setting[2,16,17]. In this series, ECMO was used in three cases and only one was discharged after transplantation. In view of this, our institution has been working vigorously to increase circulatory support results and usage.

Another approach to improve the supply of organs is pediatric HTx in ABO incompatibility system, which has already been successfully performed in patients under one year, with results similar to the ABO compatible HTx[2,18].

It is known that the indication for circulatory support as bridge to transplantation in the pediatric population has been increasing and reached a quarter of cases currently on the ISHLT report[19].

Immunosuppression and Rejection

The immunosuppressive regimen has evolved over time, especially with the advent of monoclonal antibodies and plasmapheresis. However, our protocol basically consists of the use of calcineurin inhibitor and cytostatic. The initial calcineurin inhibitor is cyclosporine, and in patients with refractory or late rejection and adverse effects to cyclosporine, tacrolimus was used as salvage therapy.

Rejection was responsible for 25% of deaths. The diagnosis of rejection is performed by clinical evaluation with noninvasive methods such as clinical symptoms of irritability, fatigue, heart failure, arrhythmias, electrocardiographic and echocardiographic changes. Gallium 67 scintigraphy and BNP (brain natriuretic peptide) have been useful in contributing to confirm the diagnosis[7].

The endomyocardial biopsy is the gold standard for diagnosis. At the beginning of the experiment, the protocol consisted of performing it only in cases refractory to treatment. More recently, the protocol has been more invasive and biopsy is routinely done in the first and second months of follow-up, and at the time of suspected rejection and/or control treatment.

Infection

Our infection rate was significant with a predominance of bacterial infections and sepsis with pulmonary involvement, which reflects the findings in most services. However, policies to control infection in these immuno-compromised patients need to be more efficient as they may have a positive impact on survival. In this series of patients, infections were responsible for 25% of mortality.

Graft vascular disease

In this series, the incidence of this complication was 7.4% in 10 years of follow-up. The increase in BNP, in addition to its already known relationship with rejection, seems to be associated with the occurrence of GVD[7]. In our department, we have made aggressive attempts to perform coronary angiography and/or coronary angiotomography to have and early diagnosis.

Lymphoproliferative disease

The occurrence of lymphoproliferative disease, especially in children, may be related to soroconversion of the Epstein-Barr virus post-HTx. However, the exact incidence of this disease is unknown, ranging from 2 to 20%[8].

Our treatment protocol consists in the reduction of the immunosuppressive therapy and, in selected cases, the use of monoclonal anti-CD 20 antibody (rituximab).

This complication can be lethal. In eight patients in our study, mortality was 25%, with all of those deaths being directly related to the complication.

Survival

As far as the known severity and complexity of these patients, data show that we can expect satisfactory results in the medium and long-term follow-up of children who are submitted to HTx in our institution.

Most studies show that despite a higher immediate mortality, the survival of patients below one year is better[2,19]. This did not occur in our series, in which survival did not vary with age. We attribute this to the small number of infants (11 cases).

The 30-day mortality in our center was satisfactory and comparable to that reported recently by North-American researchers[2]. Most importantly, that study reported a high incidence of hypoplastic left heart, unlike our experience. In our hospital, it was possible to transplant only two HLHS patients.

Late survival at 15 years is around 50% in international records.

Our data show a slightly lower survival rate (44.4%); however, with median survival around 11 years, close to the international results[19].

CONCLUSION

Our results reinforce the therapeutic success of heart transplantation for the treatment of these patients in our country.

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Authors' roles & responsibilities	
LAM	Data analysis, preparation of the manuscript and final approval
EA	Data collection and analysis and preparation of the manuscript
LFC	Data collection and analysis
ALT	Data collection and preparation of the manuscript
CT	Data collection and analysis
JGP	Data collection and analysis
AC	Data collection and analysis
MBJ	Data analysis and preparation of the manuscript

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