

# Good long-term survival after paediatric heart transplantation

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## ABSTRACT

**INTRODUCTION:** The brain-death criterion was introduced in Denmark in 1990. The first Danish paediatric heart transplantation (HTx) was performed at Copenhagen University Hospital, Rigshospitalet, in Copenhagen in 1991. We describe our experiences during the first 20 years with paediatric HTx.

**MATERIAL AND METHODS:** This was a retrospective study of 37 paediatric patients (< 18 years) who were listed for HTx from 1991 to 2011.

**RESULTS:** A total of 26 of the 37 children listed underwent HTx, nine due to congenital heart disease (CHD) and 17 due to cardiomyopathy (CM). Ten patients died while being on the waiting list. One patient was withdrawn from the list due to spontaneous improvement. A total of 21 patients remain alive. Survival was 92% after five years and 82% after ten years. We had two early (CHD) and three late (CM) deaths. Complications were few, but significant. Early acute rejection occurred in seven patients, whereas one patient with repeated late episodes of acute rejection died from graft failure 5.5 years after HTx. We found a time-related progressive deterioration in renal function. Two patients underwent renal Tx, two others died while being on dialysis. Cardiac allograft vasculopathy occurred in three patients, two of whom died. The third remains alive today, 19 years after HTx.

**CONCLUSION:** Our paediatric HTx results are comparable with those of larger international centres and consistent with true long-term survival.

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**TRIAL REGISTRATION:** not relevant.

Heart transplantation (HTx) is an established treatment option for paediatric patients with end-stage heart failure [1]. The dominant diagnosis in adult HTx-patients is cardiomyopathy (CM), whereas congenital heart disease (CHD) constitutes a second major group in paediatric HTx populations. The brain-death criterion was introduced in Denmark in 1990. The first adult HTx was performed at Copenhagen University Hospital, Rigshospitalet (RH), the very same year, whereas the first paediatric HTx was performed one year later. Since then, another 25 paediatric HTx procedures have been performed at RH. We describe our first 20 years with paediatric HTx at RH.

## MATERIAL AND METHODS

### Patients

A total of 37 paediatric patients (< 18 years), who were listed for HTx during the 20 years from 1 March 1991 to 28 February 2011, were included in this retrospective study. Patients were identified in the Scandinavian Transplant Registry. Data were collected from the prospective database of the Cardiothoracic Department at RH and from patient files.

### Medical treatment

Induction therapy was initiated with a high dose of corticosteroid and anti-thymocyt globulin. Long-term immunosuppression therapy was a combination of corticosteroids, cyclosporin and azathioprine. Since 1995, newer immune-modulating drugs such as tacrolimus and mycophenolate mofetil have increasingly been used as substitutions for cyclosporine and azathioprine, respectively; and a number of patients have been weaned from chronic steroid treatment. Severe episodes of acute rejection were treated with methylprednisolone and milder degrees of rejection were treated with an increase in the basic immunosuppressive treatment. Myocardial biopsies (MYBI) served to detect rejection in these cases. Antiviral prophylaxis with ganciclovir (valganciclovir) was used during the first three months after transplantation and long-term sulfamethoxazol as prophylaxis against pneumocystis carinii infections. Statins have been introduced in an attempt to reduce cardiac allograft vasculopathy (CAV), a special form of diffuse arteriosclerosis occurring in the vessels of transplanted hearts [2], and these are now routinely used in all children older than five years.

### Follow-up program after paediatric heart transplantation

Patients were evaluated post HTx with MYBI, myocardial scintigraphy and echocardiography. The adult follow-up programme was tailored to the individual patient's age, the feasibility of venous access and was modified in accordance with previous acute rejection episodes. Patients were routinely seen for clinical evaluation every month during the first year and after that on a three-month basis. Electrocardiography, echocardiography and exercise tests were performed annually. Supplementary

## ORIGINAL ARTICLE

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investigations (MYBI), Cr-ethylene diamine tetraacetic acid clearance, myocardial scintigraphy and coronary angiography (patients > 18 years)) were performed according to individual evaluation. Myocardial scintigraphy was used as a screening method for significant CAV [3]. If CAV was suspected, coronary arteriography was performed.

### Statistical methods

Data are stated as medians and ranges. The Mann-Whitney U test and Fisher's exact test were used to compare groups. Spearman's r-test was used for analysis of correlation.

*Trial registration:* not relevant.

### RESULTS

Indication for HTx was terminal heart failure and all patients received maximal anti-congestive treatment. During the 20-year study period, 37 patients were listed for HTx and one for re-HTx (Table 1) and 26 were transplanted. One patient was withdrawn from the list due to improvement in the clinical condition and remains alive at present, two years later. Two of the patients who died while waiting were placed on extracorporeal membrane

### ABBREVIATIONS

CAV = cardiac allograft vasculopathy  
 CM = cardiomyopathy  
 CHD = congenital heart disease  
 ECC = extracorporeal circulation  
 ECMO = extracorporeal membrane oxygenation  
 GFR = glomerular filtration rate  
 HTx = heart transplantation  
 ICU = intensive care unit  
 ISHLT = International Society for Heart and Lung Transplantation  
 LVAD Left = ventricular assist devices  
 MYBI = myocardial biopsies  
 RH = Rigshospitalet

oxygenation (ECMO). Two patients died suddenly outside the hospital and the last four died due to combined heart-multi-organ failure. Gender, age at listing, time on waiting list, body surface, body weight and type of heart failure are shown in Table 1. None of these parameters had any significant influence on whether the patient was transplanted. Younger age and low body weight, however, may have had a significant influence that was not detected due to small sample size ( $p = 0.1$  and  $0.16$ ).

A total of 26 paediatric patients underwent HTx during the 20-year study period (19 boys, median age

TABLE 1

Demographics for patients listed for heart transplantation..

	All (n = 37)	+HTx (n = 26)	Non-HTx (n = 11)	p values <sup>a</sup> (+HTx vs non-HTx)
Male/female, n	11/26	7/19	4/7	0.42 <sup>b</sup>
CHD/CM, n	14/23	9/17	5/6	0.40 <sup>b</sup>
Age at listing <sup>c</sup> , years	6.7 (0.5-17.8)	10.7 (0.5-17.8)	3.9 (0.9-17.3)	0.10
Time on waiting list to HTx or death <sup>c</sup> , days	72 (4-662)	66 (4-662)	80 (4-511)	0.75
Body surface <sup>c</sup> , m <sup>2</sup>	0.86 (0.32-1.97)	1.07 (0.32-1.97)	0.59 (0.39-1.7)	0.19
Body weight <sup>c</sup> , kg	20.8 (6-67)	27.5 (6-67)	14.0 (6-67)	0.16

CHD = congenital heart disease; CM = cardiomyopathy; HTx = heart transplantation; +HTx = patients who received a donor heart; Non-HTx = patients who did not receive a donor heart.

a) p values when comparing +HTx with non-HTx were found using Mann-Whitney test (age, waiting-time, body surface, body weight) or by Fisher's test; b) Gender CHD/CM; c) Data are given as median (and range).

TABLE 2

Per- og postoperative data for heart transplanted children at Rigshospitalet in the 20-year period 1991-2011: donor ischaemic-time, time on extracorporeal circulation, time in ventilator, time in intensive care unit, deaths, survival-time, acute rejection and cardiac allograft vasculopathy.

	All HTx pts (n = 26)	CHD (n = 9)	CM (n = 17)	p values (CHS vs CM)
Donor ischaemic time <sup>c</sup> , min.	251 (81-390)	301 (90-390)	229 (81-311) <sup>a</sup>	0.12
Time on ECC <sup>c</sup> , min.	150 (100-526)	224 (106-526)	150 (100-258)	0.12
Time on ventilator <sup>c</sup> , days	2 (1-33)	5 (1-32)	1 (1-33)	0.09
Time in ICU <sup>c</sup> , days	5 (2-48)	6 (3-48)	5 (2-37)	0.13
Deaths, n	5	2	3	0.58 <sup>b</sup>
Survival-time <sup>c</sup>	11.3 yrs (6 days-20 yrs)	11.6 yrs (6 days-16.8 yrs)	11.1 yrs (0.4-20 yrs)	0.27
Acute rejection, n	12	2	10	0.08 <sup>b</sup>
CAV pts, n	3	0	3	0.29 <sup>b</sup>

CAV = cardiac allograft vasculopathy; CHD = congenital heart disease; CM = cardiomyopathy; ECC = extracorporeal circulation; HTx = heart transplantation; ICU = intensive care unit; pts = patients.

a) Donor ischaemic time was not available for four patients, thus: n = 13; b) Fishers exact p.; c) Data are given as median and range.

10.7 (0.5-17.8) years (Table 1). All patients with CHD had undergone previous heart surgery (2-5 procedures). One patient had an implantable defibrillator. Four patients, all with CM, were treated with mechanical circulatory support before HTx: one on ECMO for three days, two on left ventricular assist devices (LVAD), both for four days, and one was treated with an implantable support system (HeartMate XVE) for ten months as a bridge to HTx. Donor hearts came from Denmark (n = 12), Sweden (n = 4), Norway (n = 4), Finland (n = 2), Germany (n = 2), Belgium (n = 1) and Switzerland (n = 1). Donor age ranged from one to 61 years (median 12.5 years). For all but one, the body-weight ratio between donor and recipient (donor/recipient) was larger than one (median 1.43, range 0.8-3.2).

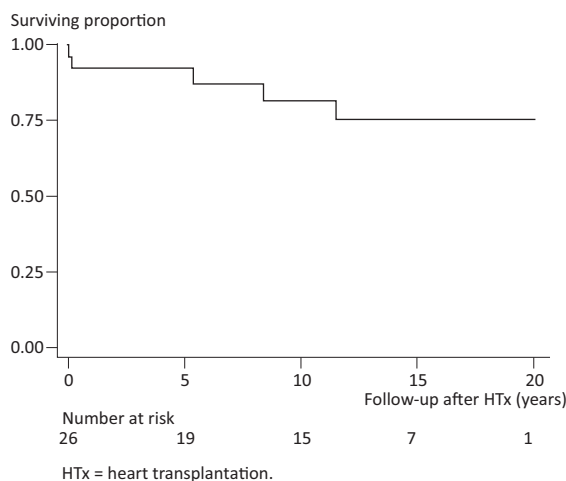
Perioperative data are shown in **Table 2**. No difference could be demonstrated between CHD and CM patients for the following per- and postoperative parameters: mortality, time of graft ischaemia, time on extracorporeal circulation (ECC), time on ventilator or time in intensive care unit (ICU). A trend, however, for a more difficult perioperative course in CHD than in CM patients was noted for graft ischaemia time, ECC, ventilator time and intensive care unit time (0.09-0.13) (risk of type II-statistical error).

A total of 21 of 26 patients remain alive. Survival calculated by the Kaplan-Meier method is 92% after five and 82% after ten years (**Figure 1**). We had two early deaths, both in patients with single ventricle anatomy and a Fontan circulation. One patient had undergone four previous heart surgical procedures and had developed thrombosis in the pulmonary arteries after contraceptive treatment. Surgery was extremely difficult due to an abnormal anatomy, surgical adhesions, significant bleeding problems and long graft ischaemia time. The child was placed on LVAD, but died six days after HTx. Another patient had moderate renal failure pre-HTx that did not improve after HTx, and the patient died from multi-organ failure 45 days later. The other three patients died 5.5, 8 and 11.5 years after HTx. No patients were re-transplanted, but the patient who died 11.5 years after HTx was listed for re-HTx due to CAV.

Eight patients had 13 episodes of severe (H3R) acute rejection. Eleven of these episodes occurred in the first six months after HTx. One patient had two very late rejection episodes, probably due to non-adherence to the immunosuppressive treatment, and died from graft failure 5.5 years after HTx. There was a tendency ( $p = 0.08$ ) towards an increased risk of acute rejection in the CM patient group.

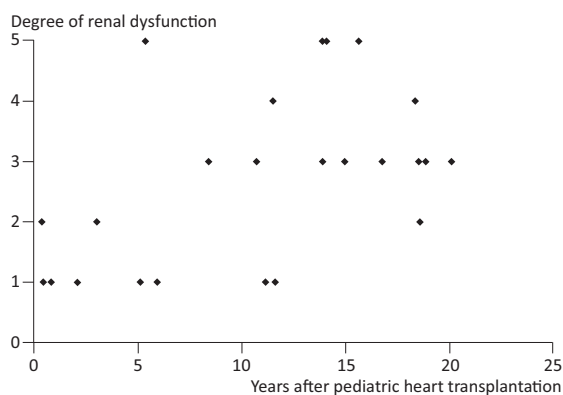
Three patients (all > 18 years) developed CAV, all verified by coronary angiography, and two of these died 5.5 and 11.5 years after HTx. The third patient remains alive today, nearly 19 years after HTx.

**FIGURE 1**



Kaplan-Meier plot showing survival after paediatric heart transplantations performed in the period 1991-2011 in Copenhagen.

**FIGURE 2**



Degree of renal dysfunction as a function of time after paediatric heart transplantation. The renal function was evaluated by  $^{51}\text{Cr}$  EDTA-clearance as glomerular filtration rate.

The numbers 1-5 signify:

- 1) GFR > 80 ml/min.
- 2) 80 > GFR > 60 ml/min.
- 3) 60 > GFR > 30 ml/min.
- 4) 30 ml/min. > GFR
- 5) No renal function.

Note: The two patients who died six and 45 days after HTx, respectively, are not included in the graph.

EDTA = ethylenediaminetetraacetic acid.

GFR = glomerular filtration rate (ml/min./1.73 m<sup>2</sup>).

HTx = heart transplantation.

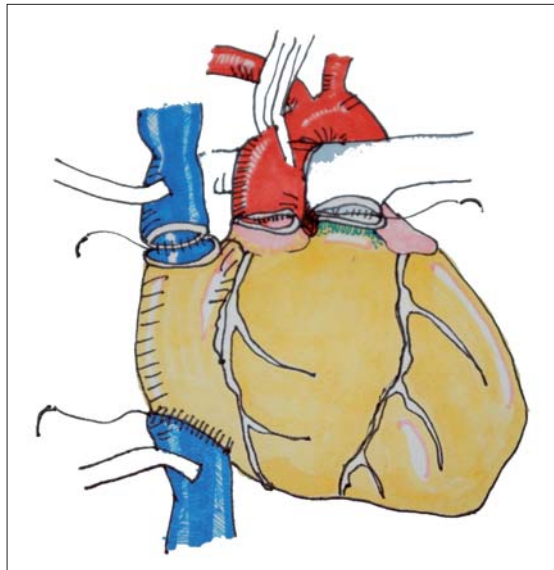
All patients experienced a significant time-related progressive deterioration in renal function ( $p < 0.05$ ) (**Figure 2**). Four patients developed terminal renal failure, two underwent renal transplantation and the two others died while on dialysis.

One patient underwent tonsillectomy due to post-transplant lympho-proliferative disease (PTLD), but no other malignancies were noted.

## DISCUSSION

The first paediatric HTx in Denmark was performed at

Suture lines in heart transplantation with cava-cava anastomoses.



the RH in March 1991. This patient remains alive today, 20 years later. Since then, another 25 paediatric patients have undergone HTx at the RH. Survival calculated by Kaplan-Meier method is 92% after five and 82% after ten years. These results are at par with those reported from larger centres around the world [1, 4-6], although comparison of results from low- and high-volume centres is difficult. In their 2010 report [1], the International Society for Heart and Lung Transplantation (ISHLT) registry reported a 14-year median survival time (50% remain alive) for HTx-children. We experienced two early deaths, both in patients with single-ventricle anatomy. Both cases clearly illustrate the difficulties in paediatric HTx-patients with CHD: complex anatomy, surgical adhesions, significant operative bleeding and pulmonary embolism with post-operative increased pulmonary vascular resistance. We found a tendency for CHD patients to have a longer time of surgery, longer graft ischaemia time and post-operative stay in the ICU, although this difference did not reach statistical significance ( $p$  values: 0.09-0.13). One of the patients, who died early after HTx, had a significantly reduced renal function pre-HTx. This was evaluated to be potentially reversible. However, the renal function did not improve after HTx and the patient died from multi-organ failure. Despite this, the recommendations for such a patient would still be to list the patient for isolated HTx, as moderate to severe renal failure has been shown to be at least partly reversible after improvement of the circulation [7].

A total of 37 patients were listed for HTx during the 20-year period (0.75 patients per million per year), which is significantly lower than in a recent Swedish report for a similar period [8]. This difference may be explained by a preference in Copenhagen to perform palliative heart surgery instead of listing the patient for

HTx, or by a more restrictive policy for listing patients for HTx. Thus, in the Swedish report [8], 10% of the HTx-listed patients were withdrawn from the waiting-list due to clinical improvement, whereas only one of 37 (3%) HTx-listed patient was withdrawn from our list. Ten of 37 patients died on the HTx waiting-list, which is equivalent to Swedish findings [8].

Matching donor-recipient size in a paediatric population is different from doing so in adults. Hearts in patients with some types of either CHD or CM can be significantly dilated, and it was possible to transplant hearts from donors that were more than three times bigger than the recipient, thus increasing the pool of recipient hearts. We could not detect that smaller children had a significantly lower chance of getting a heart ( $p = 0.16$ ), but this may be due to the small sample size (risk of type II statistical error).

An increased use of mechanical supports systems (short-term LVAD, ECMO, Berlin Heart, Heart Mate) might have augmented the number of performed HTx [9, 10]. Four patients who received a donor-heart and two who did not were supported by one of these systems. Two other patients died while being on the HTx waiting-list, most likely due to malignant arrhythmias. In such patients, defibrillator implantation should be considered [11].

Acute rejection episodes have been a problem through the entire HTx era. We found a moderate number of acute rejection episodes, especially during the first year after HTx, with indication for intensified immunosuppressive treatment. One patient had unexpected acute rejection episodes several years after HTx, probably due to non-adherence to the immunosuppressive treatment. Non-adherence is, unfortunately, a well-known problem in adolescents and young adults after transplantation [12].

Progressive renal dysfunction is recognised in adult as well as in paediatric HTx populations [1, 13], and we demonstrated a progressive, time-related renal dysfunction in the paediatric HTx patients. Four of the 24 long-term survivors (17%) suffered from severe renal dysfunction and needed dialysis or renal transplantation. In the ISHLT registry, 5% of the patients required renal Tx or dialysis within ten years after HTx [1]. Renal dysfunction is mainly caused by the nephrotoxic effect of the calcineurin inhibitors cyclosporine and tacrolimus [13]. An aggressive immunosuppressive treatment may explain the rather low number of acute rejection episodes and the seemingly higher frequency of renal dysfunction seen in our patients.

CAV has had a major impact on long-term survival in the paediatric HTx population [1]. We found CAV, verified by coronary angiography, in three of the 24 long-time survivors. None of these have had re-vascularisa-

tion procedures, which is often not feasible due to the diffuse nature of CAV [2]. The pathogenesis of CAV is not well-understood, but seems to be multi-factorial, induced by a combination of rejection and more conventional atherogenic factors [2].

A few studies have reported a higher occurrence of post-transplant lympho-proliferative disease [14, 15] than that found in the present study, i.e. one out of 24 long-term survivors. However, our findings are similar to those in the ISHLT registry [1].

Special ethical considerations should be taken into account when evaluating the possible indication for HTx in children with heart disease [16]. Thus, is it relevant to perform HTx with a median survival time of 15 years well knowing that the only life-saving treatment at this time may be re-transplantation? The results from re-HTx are inferior to those observed after the primary HTx. However, a recent multi-centre study of re-HTx patients, in which patients were separated into those with “early” versus “late graft failure”, demonstrated that the re-HTx results for patients with “late graft failure” were not significantly different from first-time HTx [17]. Another important issue is renal function. Thus, after combined heart and kidney transplantation, results are inferior to those seen after single HTx [18]. Finally, problems such as lack of donor hearts and a mortality of 30% while patients are on the waiting-list furthermore emphasize the difficult ethical considerations.

However, there has been an improvement in the HTx-survival regarding the different time-eras [1]. This seems primarily to be caused by improvements obtained in the peri-operative period (surgery, patient-selection, post-operative intensive care). Thus, early survival has increased, whereas the chronic survival decay curve has largely remained unchanged during the past decades [1]. The greatest challenge is still the lack of donors. A possible solution would be development of fully implantable mechanical devices with a longer duration suitable for the paediatric population.

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**CONFLICTS OF INTEREST:** none

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