

## Long-term Results of Pediatric Heart Transplantation

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**Objective:** We retrospectively reviewed 104 consecutive patients who underwent orthotopic heart transplantation between November 1989 and February 2004.

**Patients and Methods:** From November 1989 to February 2004, the total number of heart transplantations were 1,340 cases at our institute. One hundred four (7.8%) of these 1,340 patients were pediatrics. Average age was 6.2 years, ranging from 4 months to 16 years. The cause of heart disease before transplantation was: idiopathic dilated cardiomyopathy (DCM) in 74 patients (71%), and congenital heart disease (CHD) in 30 (29%).

**Results:** Hospital mortality rate was 14.4% (15 patients). Late complications were rejection in 23 (22.1%), infection in 11 (10.6%), gingival hyperplasia in 28 (26.9%), hypertension in 22 (21.1%), coronary artery disease (CAD) in 12 (12.5%), graft failure in 11 (10.5%), and malignancy in 2 (1.9%). Late mortality occurred in 11 (10.6%) patients. Causes of death were sudden death in 2 (1.9%), CAD in 3 (2.8%), graft failure in 1 (1.0%), acute rejection in 4 (4.6%), and infection in 1 (1.0%). Actuarial survival rates in pediatrics at 1, 5, 10 years were 82%, 80%, and 78%, respectively. On the other hand, actuarial survival rates in adults at 1, 5, 10 years were 78%, 75%, 59%, respectively.

**Conclusion:** Heart transplantation for pediatrics is an effective therapy with acceptable morbidity and mortality. The long-term survival results in pediatrics are comparable to those of adult heart transplantations. However, the actuarial survival rate in pediatrics after 10 years is significantly better than in adults' cases. Renal function in pediatric heart transplantation recipients treated with cyclosporine remains stable during long-term follow-up. (*Ann Thorac Cardiovasc Surg* 2005; 11: 386–90)

**Key words:** heart transplantation, pediatrics, rejection, congenital, cardiomyopathy

### Introduction

Heart transplantation is becoming a more established form of treatment for patients with end-stage heart disease in

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both, adults and children. At our institute, the heart transplantation program was started in 1989. Between November 1989 and February 2004, a total number of 1,340 patients underwent orthotopic heart transplantation. 104 (7.8%) of these 1,340 patients were pediatrics. We report a single center experience with 104 children who had a heart transplantation at the Heart Center North Rhein-Westphalia, Ruhr University of Bochum, Bad Oeynhausen, Germany.

### Patients and Methods

Between November 1989 and February 2004, 104 children underwent primary orthotopic cardiac transplanta-

tion at our institute. There were 59 boys and 46 girls. The recipient age range at the time of transplantation was 2 days to 16 years (mean 6.2 years). Nineteen (18.3%) patients were under the age of 1 year. The cause of heart disease before transplantation was: idiopathic dilated cardiomyopathy (DCM) in 74 (71%) patients and congenital heart disease (CHD) in 30 (29%). Follow-up time after transplantation is 1 month to 13.7 years (mean 5.2 years). Waiting time range for transplantation was 30 days to 749 days (mean 69 days). Application of mechanical circulation support (MCS) was 29 children because of end-stage heart disease before heart transplantation. Thirteen of 29 (44.8%) patients were successfully bridged to heart transplantation (9 patients) or weaned (4 patients) off their devices after recovery. Five of 9 transplanted children were in need of left ventricular assist devices (LVAD), three patients were in need of biventricular assisted devices (BVAD), and extracorporeal membrane oxygenation (ECMO) was needed by one patient. For small children (under 12 kg) we selected the ECMO for mechanical circulatory support, and older children we selected para-corporeal circulation (LVAD or BVAD). Waiting time on MCS was 9 days to 258 days (mean 89 days).

The donor age range was 1 day to 31 years (mean 6.4 years). Cause of brain death was trauma in 56 (53.8%) patients, hypoxia in 23 (22.1%), cerebral bleeding in 11 (11.0%), cerebral tumor in 5 (4.8%), other in 9 (8.1%). Total ischemic time ranged from 95 to 340 minutes with a mean of 211 minutes. Donor hearts harvesting was performed with Bretschneider's histidine-tryptophane-ketoglutarate (HTK) crystalloid cardioplegic solution.<sup>1,2)</sup>

We studied allograft function assessed by shortening fraction and left ventricular end diastolic pressure measured by echocardiography, abnormality of the coronary arteries through coronary angiography, complications of immunosuppression and their daily living. An actuarial survival curve was calculated using the Kaplan-Meier survival analysis and was compared using the log-rank test.

Renal function was monitored with regular creatinine levels, creatinine clearance was performed if there was any evidence of deteriorating renal function.

### Immunosuppression Therapy

Our immunosuppression protocol is based on the standard triple-drug immunosuppression with a calcineurin inhibitor (cyclosporine), prednisone and an antimeyabolite (azathioprine). Preoperative therapy is 0.25 mg/kg cyclosporine, 3-4 mg/kg azathioprine and 125 mg meth-

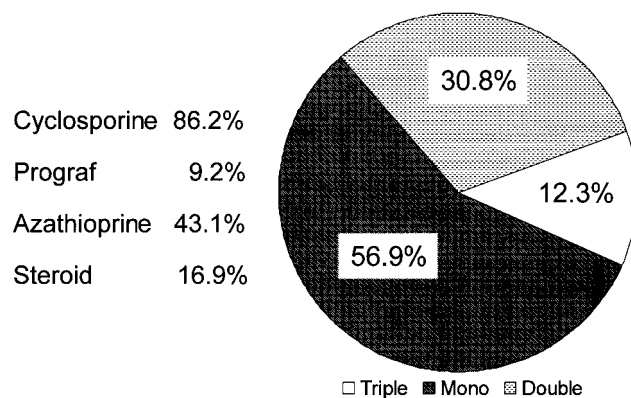


Fig. 1. Posttransplant immunosuppression therapy for long-term survivors.

ylprednisolone intravenously. During the intraoperative period, 125 mg methylprednisolone is given intravenously before aortic crossclamp removal. In the early-postoperative period, 125 mg methylprednisolone is given intravenously 3 times a day over a period of 3 days. After that, methylprednisolone is changed to oral steroids. After the operation, patients continue receiving 0.1-0.2 mg/kg cyclosporine intravenously and also started to receive oral doses of cyclosporine A (CSA). A level of 300-400  $\mu\text{g/l}$  is achieved and maintained. After a couple of days, the intravenous cyclosporine is tapered off over the next few days. Azathioprine is applied 1-4 mg/kg intravenously. If the patient has no rejection episodes, steroids are discontinued in the late postoperative period. Longterm-immunosuppression therapy is based on 4-6 mg/kg cyclosporine azathioprine 0-2 mg/kg oral. Azathioprine dosage is adjusted to keep the white blood cell count greater than 4,000 (Fig. 1).

### Results

The hospital mortality rate was 14.4% (15 patients). Cause of death was: primary graft failure in 3 patients, acute rejection in 3, LOS in 3, mismatch in 2, sepsis in 2, bleeding in 1 and multiple organ failure (MOF) in 1. Late complications were rejection in 23 (22.1%), infection in 11 (10.6%), gingival hyperplasia in 28 (26.9%), hypertension in 22 (21.1%), coronary artery disease (CAD) in 12 (12.5%), graft failure in 11 (10.5%), and malignancy in 2 (1.9%).

Seventy-eight percent of patients had no rejection, and it occurred once in 15%, twice in 6%, 3 times in 2%, and over 4 times in 2%, respectively.

Nephrotoxicity is one of the most common complications of immunosuppression therapy after heart transplan-

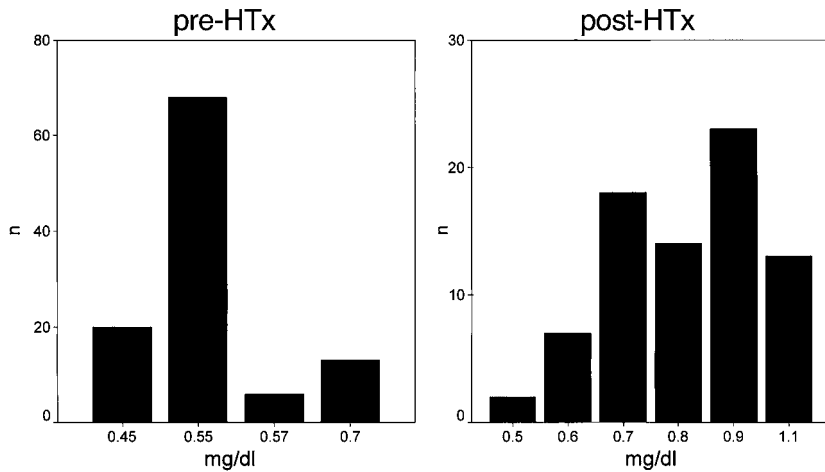


Fig. 2. The average serum creatinine levels in pediatric recipients.

tation, but none of the patients in this series had critical renal dysfunction. However, creatinine levels have shown a tendency to rise after heart transplantation (Fig. 2). Late mortality was 11 (10.6%) patients. Cause of death was sudden death in 2 (1.9%), CAD in 3 (2.8%), graft failure in 1 (1.0%), acute rejection in 4 (4.6%), and infection in 1 (1.0%).

CAD developed in 12 (12.5%) patients in this series. Three of 12 patients died following this complication, one had a re-transplantation. Coronary angiography was performed in 63 of 83 patients (76%) who are long-term survivors. Angiography was performed at 1.1 to 13.7 years (mean 5.2 years) after heart transplantation. The results

were no critical stenoses in 61.3%, mild narrowing in 23.7%, and severe CAD in 15%.

Allograft function was measured by echocardiography, 98% of the patients had good systolic function, but disturbed diastolic function at 2, 5, 10 years were 8%, 14%, 38%, respectively.

Actuarial survival rates after transplantation in pediatrics at 1, 5, 10 years were 82%, 80%, and 78%, respectively. On the other hand, actuarial survival rates in adults were at 1, 5, 10 years were 78%, 75%, 59%, respectively (Fig. 3).

Social activities of all survivors after heart transplantation are school: 65.8%, working: 17.7%, home: 15.1%, hospital: 1.4%, respectively (Fig. 4).

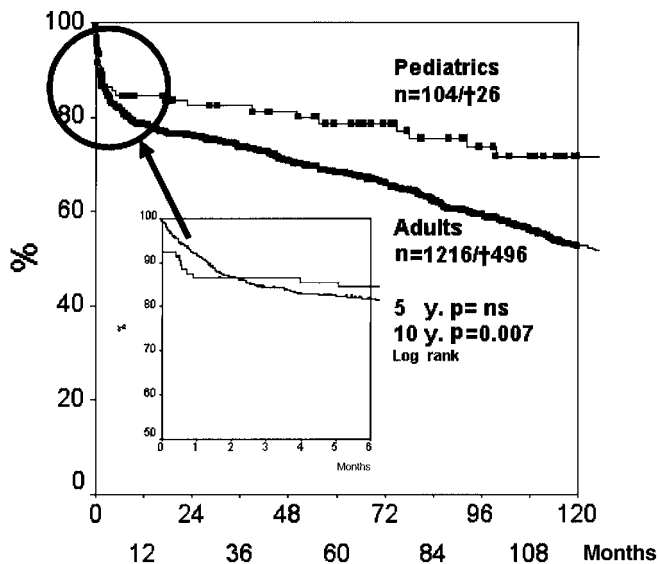


Fig. 3. Actuarial survival curves after heart transplantation (pediatrics vs. adults). ns, not significant; †, death.

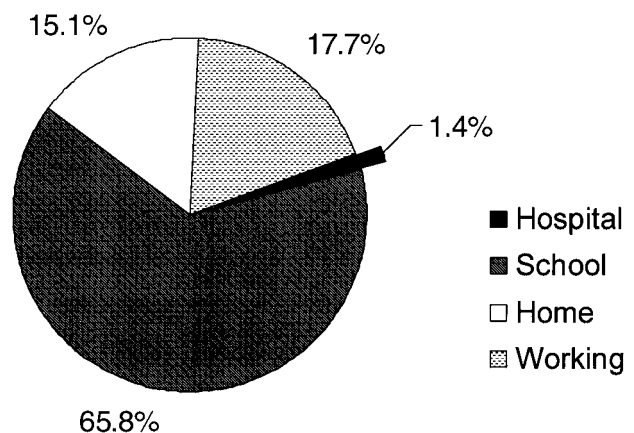


Fig. 4. Social activity after pediatric heart transplantation.

## Discussion

As orthotopic heart transplantation has become an established modality in the treatment of end-stage heart disease. Recently, there have been some reports of long-term results after pediatric heart transplantation.<sup>3-5</sup> At our institute the actuarial survival rates after transplantation in pediatrics at 1, 5, 10 years are 82%, 80%, and 78%, respectively. On the other hand, actuarial survival rates in adults at 1, 5, 10 years are 78%, 75%, 59%, respectively. In our experience, the results of pediatric heart transplantation at 1, 5 years are comparable to those of adults' cases. But the actuarial survival rate in pediatrics at 10 years is significantly better than in adult recipients ( $p=0.007$ ). We think that there is a lower rejection rate in pediatric than in adult cases (pediatric vs. adult: 1.7 times/year vs. 2.8 times/year). Survival rates up to two months are better in adults than in pediatrics, however, after two months the rates are contrary (Fig. 2). In our opinion this is because of higher earlier mortality in congenital patients than in DCM patients, as will be described later.

The introduction of cyclosporine in 1980 as the principal immunosuppressive agent in heart transplantation has been associated with improved results and a dramatic increase in the number of heart transplantation performed worldwide. However, cyclosporine related nephrotoxicity remains one of the long-term limitations of cardiac transplantation at any age.<sup>6</sup> Previous reports of heart transplantation recipients have suggested that renal function decreases during the first year of transplantation and remains moderately depressed at long-term follow up.<sup>7,8</sup> On the other hand, cyclosporine therapy does not progressively impair glomerular or tubular functions in pediatrics.<sup>9,10</sup> In our series, renal dysfunction is still mild and we have had no patients who require dialysis. However, creatinine levels have shown a tendency to rise after heart transplantation, therefore, we think they need a careful follow-up.

Coronary atherosclerosis has been cited as the major cause of graft loss after heart transplantation in adults in both, the precyclosporine and the cyclosporine eras.<sup>11,12</sup> Coronary angiography was performed in 63 of 83 patients (76%) who are long-term survivors. Angiography was performed at 1.1 to 13.7 years (mean 5.2 years) after heart transplantation. There were no findings in 61.3%, mild CAD in 23.7, and severe CAD in 15.0%. The incidence of CAD in this series appears to be similar to that in other reports of pediatrics and have lower incidence rates than

in the adult patients.<sup>13</sup> Presently, coronary angiography is the only reliable way to diagnose CAD, but even this examination does not show early disease or concentric narrowing.<sup>14</sup> Several methods of treatment for CAD after transplantation have been attempted, but percutaneous transluminal coronary angioplasty (PTCA) is usually ineffective because of the diffuse lesions.<sup>15,16</sup> Similarly, coronary bypass grafting is not effective and has not been attempted because of the distal obliterative pathology in transplant recipients.

Robert et al. reported that donor ischemic time was not identified as an independent risk factor, however, longer ischemic times (>240 minutes) were highly correlated with younger age and the presence of an assist device.<sup>17</sup> In our series total ischemic time ranged from 95 to 340 minutes with a mean of 211 minutes.

The risk factor for early death after transplantation in this study seems to be hemodynamic instability before transplantation requiring long-term treatment in the intensive care unit.

We have reported that the actual survival in patients with DCM was better than in patients with CHD.<sup>18</sup> Especially, in cases of hypoplastic left heart syndrome (HLHS) patients who underwent heart transplantation had a higher early mortality than cardiomyopathy patients.

All long-term survivors have good quality of life. Over 80% patients of them have returned to normal activities for their ages. Social activities of all survivors after heart transplantation are school: 64.8%, working: 16.7%, home: 15.1%, hospital: 1.4%, respectively.

Finally, we describe the donation system in Germany. In the case of cerebral death diagnosed by two independent neurologists and the parents of the pediatric patient agreeing to organ donation, the Eurotransplant (ET) in Leiden, the Netherlands, will be informed and the donor data are registered. According to German Transplantation Law, a donor card is not necessary for donation.

## Conclusion

Heart transplantation in pediatrics is an effective therapy with acceptable morbidity and mortality. In our experience, the long-term results in pediatrics are comparable to those of adult heart transplantation. However, the actuarial survival rate in pediatrics at 10 years is significantly better than in adults' recipients. Renal function in pediatric heart transplantation recipients treated with CSA remains stable during long-term follow-up.

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