Heart transplantation for dilated cardiomyopathy

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Abstract

Between 1988 and 1994, 23 patients underwent heart transplantation for dilated cardiomyopathy. The age of the 13 boys and 10 girls was from 8 months to 16 years (mean 7.1 years). Selection criteria included failure to thrive despite maximal antifaailure treatment and/or intravenous inotrope dependence. The aetiology of cardiomyopathy was idiopathic (n=13), congenital (n=3), anthracycline induced (n=4), Barth's syndrome (n=1), and maternal systemic lupus erythematosus (n=2). The waiting period to heart transplantation ranged from one day to 147 days (mean 22 days). Maintenance immunosuppression included cyclosporin, azathioprine, and prednisolone. Follow up after transplantation was from one month to 62 months (median 27 months) with a mean actuarial survival of 95% at one year and 87% at three years. Four patients developed coronary artery disease, one of whom died as a consequence 15 months after heart transplantation. Heart transplantation has emerged as an acceptable therapeutic option, at least in the short term, for patients with dilated cardiomyopathy.

(*Arch Dis Child* 1995; 73: 447-452)

Keywords: dilated cardiomyopathy, heart transplantation, survival.

This report reviews our clinical experience with orthotopic heart transplantation for dilated cardiomyopathy, exploring the appropriate timing of transplantation and issues related to post-transplant complications including graft associated coronary artery disease, growth retardation, and renal dysfunction.

Dilated cardiomyopathy is the most common cause of end stage acquired heart disease in children and adolescents. It is characterised by a dilated, poorly functioning heart. It can be primary, that is of unknown cause, or secondary due to conditions such as viral myocarditis, storage diseases, birth asphyxia, anthracycline toxicity, connective tissue disease, incessant arrhythmias, and mitochondrial myopathy. It is a therapeutically difficult and challenging problem. Sixty to 75% of adult patients with dilated cardiomyopathy and congestive cardiac failure die within five years of presentation.^{1 2} Griffin *et al* observed a much worse prognosis in children over the age of 2 years with none surviving. The mean interval from initial presentation to death was two years.³

Heart transplantation has evolved as an

acceptable therapeutic option for adults with end stage heart disease. In infants and children with cardiomyopathy transplantation may offer the best hope for survival. Although long term data for paediatric transplant recipients remain limited, sufficient experience has accumulated in adults to suggest possible survival over decades. The 1994 registry of the International Society for Heart and Lung Transplantation has reported a 10 year actuarial survival of 45% in 26 704 adult heart transplant recipients from 251 centres.⁴ However, long term value of heart transplantation may be determined more by related complications and effects on quality of life rather than by length of survival alone.^{5 6}

Patients and methods

From April 1988 to June 1994, 23 children and adolescents underwent heart transplantation for dilated cardiomyopathy. There were 13 boys and 10 girls aged from 8 months to 16 years (mean 7.1 years). Dilated cardiomyopathy was diagnosed by echocardiographic criteria which included a left ventricular shortening fraction of $\leq 25\%$ and a left ventricular internal diameter >95 th centile for age.⁷ The aetiology was idiopathic in 13 (57%), congenital in three (13%), anthracycline induced in four (17%) caused by Barth's syndrome in one (4%), and maternal systemic lupus erythematosus in two (9%) (table 1).

Initial assessment for heart transplantation involved a four day inpatient admission during which full clinical and psychosocial evaluations were performed. Selection criteria included intractable heart failure not controlled by oral anticongestive treatment and associated with failure to thrive, and/or intravenous inotrope requirement. Contraindications included raised pulmonary vascular resistance. Evidence for this was a transpulmonary gradient greater than 15-20 mm Hg despite administration of pulmonary vasodilators (fractional inspired oxygen of 1.0, intravenous administration of prostacyclin and inhalation of nitric oxide). Severe irreversible hepatic or renal dysfunction and underlying active malignancy were other contraindications. Donor organs were selected from suitably size matched and ABO blood group compatible individuals who had suffered brain stem death and had no evidence of cardiac dysfunction. All recipients had prominent cardiomegaly, so larger donors (up to 300% of recipient body weight) were often selected. Matching for cytomegalovirus antibody status was not performed. Full HLA typing of donor and recipient together with tissue cross matching were performed retrospectively but were not used to guide clinical management.

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Accepted 12 June 1995

Table 1 Data of patients with dilated cardiomyopathy before and after heart transplantation

Case No	Age at heart transplantation (years)	Sex	LVSF (%)	TPG (mm Hg)	Waiting period (days)	Donor:recipient weight ratio	Outcome	Cause of death	LVSF at last follow up (%)
1	0.7	F	10	14	11	2.1	Alive		38
2	0.7	M	8	10	33	2.5	Alive		43
3	0.8	M	5	2	79	2	Alive		46
4	1.5	F	8	7	13	3.1	Alive		31
5	1.7	M	6	4	147	1.8	Alive		43
6	2.0	M	4	2	39	2.3	Alive		36
7	3.1	M	8	2	1	1.7	Alive		40
8	3.1	M	7	—	1	1.2	Dead	Sepsis	—
9	3.4	F	10	17	13	2.3	Alive		46
10	5.4	F	13	12	12	3.1	Dead	Coronary artery disease	—
11	5.4	M	3	8	15	1.3	Alive		46
12	6.5	F	14	8	10	1	Alive		45
13	7.6	F	10	6	7	2.2	Alive		50
14	7.9	F	9	9	7	2.1	Alive		31
15	8.6	M	11	9	44	1.6	Alive		34
16	10.9	F	9	6	21	0.7	Alive		35
17	11.3	M	7	5	11	2.2	Alive		39
18	12.0	F	14	16	23	0.8	Alive		36
19	12.1	M	7	—	3	1.5	Alive		33
20	13.7	M	8	8	1	1	Alive		18
21	13.8	F	4	4	2	0.8	Alive		48
22	15.0	M	7	2	14	0.6	Alive		27
23	16.0	M	15	7	9	1	Alive		41
Mean	7.1		8	7.5	22	1.7			38

LVSF, left ventricular shortening fraction; TPG, transpulmonary gradient.

Surgical methods for donor organ retrieval and transplantation have been previously described.⁸ Four recipients received hearts from heart-lung transplant recipients (the domino procedure).⁹ Early postoperative management has been detailed elsewhere.¹⁰ Maintenance immunosuppression comprised a triple drug regimen (cyclosporin, azathioprine, and prednisolone), with antithymocyte globulin (ATGAM, Upjohn, Crawley, UK or Lymphoglobuline – Merieux, Lyon, France) and intravenous methylprednisolone administered perioperatively and for episodes of rejection (table 2). Cyclosporin dose was adjusted to maintain the whole blood concentration between 150–300 µg/l (high performance liquid chromatography (HPLC) method) and to preserve adequate renal function (serum creatinine and urea). Azathioprine was administered to a maximum of 2 mg/kg/day to maintain the total white cell count above $5 \times 10^9/l$. Prednisolone was started on day 3 at 1 mg/kg/day in divided doses tapering to 0.2 mg/kg/day by six weeks. Children were converted to an alternate day steroid regimen by six months after transplant if tolerated.

Co-trimoxazole (24 mg/kg three days/week) was administered indefinitely as prophylaxis for *Pneumocystis carinii* pneumonitis, and nystatin suspension or amphotericin lozenges were also given long term. Acyclovir (600 mg/m²/day) was prescribed for patients with a history of herpes simplex virus labialis. Patients with cytomegalovirus mismatch were treated with gancyclovir (10 mg/kg/day intravenously) if they developed evidence of clinical cytomegalovirus disease. Cytomegalovirus immunoglobulin and prophylactic gancyclovir were not routinely administered. In those mismatched for toxoplasma status, pyrimethamine (6.25–25 mg daily according to weight) and folic acid (15 mg daily) were prescribed for six weeks after transplant.

Older children and adolescents underwent routine endomyocardial biopsies. We performed these weekly for one month, every two

weeks in the second month, monthly up to six months, and 3–6 monthly thereafter. Initially, we employed the Billingham criteria for determination of presence and severity of rejection.¹¹ Subsequently, we used the International Society for Heart and Lung Transplantation grading.¹² Rejection surveillance in infants and younger children was non-invasive using suggestive clinical signs such as fever, lethargy, tachycardia, and weight gain. We monitored electrocardiograms serially for the development of new arrhythmias, change in axis, or a drop in summation of voltages (R+S complexes in leads I, II, III, V1, and V6). Systolic and diastolic left ventricular function was evaluated by echocardiography. Changes supporting a diagnosis of rejection included a decrease in left ventricular shortening fraction, increase in left ventricular wall thickness, development of a pericardial effusion, or shortening of isovolaemic relaxation time. We performed endomyocardial biopsy in these younger patients if non-invasive criteria were inconclusive or there was poor response to treatment. Rejection was treated with intravenous methylprednisolone (10 mg/kg/day) for three days followed by a reducing oral prednisolone course (starting at 1 mg/kg/day). For rejection not responsive to repeat courses of methylprednisolone, a further course of cytolytic treatment was administered. A 'rejection episode' was recorded after a treated incident. Rejection rates were defined as the average number of episodes of rejection per patient during the first three months and in the subsequent nine months after heart transplantation.

After transplant, we routinely collected blood, urine, and throat cultures for bacteria, viruses, and fungi as well as viral serology for cytomegalovirus, herpes, varicella, and Epstein-Barr virus. An 'infection episode' was diagnosed in the presence of clinical symptoms, positive cultures, or rise in serological titres and improvement after appropriate antimicrobial treatment. Infection rates were

Table 2 Immunosuppression regimen for heart transplantation

Treatment	Preoperative	Perioperative	Postoperative
Cyclosporin	5–10 mg/kg	–	5–50 mg/kg/day*
Azathioprine	2 mg/kg	2 mg/kg/day	0.5–2 mg/kg/day†
Methylprednisolone	–	10 mg/kg 12 hours×2, 2 mg/kg 8 hours×3	10 mg/kg/day×3 for acute rejection
Antithymocyte globulin	–	0.5 mg/kg/day×3‡	0.5 mg/kg/day for severe recalcitrant rejection
Prednisolone	–	–	0.1–1 mg/kg/day (maintenance)

*Cyclosporin administered via the enteral route. Dose adjusted to maintain a whole blood concentration of 150–300 µg/l (HPLC method). †Dose adjusted to maintain the total white cell count above $5.0 \times 10^9/l$. ‡Dose adjusted to reduce total T cell count to $0.1–0.2 \times 10^9/l$.

defined using the same criteria as for rejection.

We instituted shared care as early as practicable with the referring paediatrician and/or cardiologist. Review was initially weekly gradually extending to three monthly intervals. At each follow up a detailed clinical examination was performed with height, weight, and blood pressure recorded. Electrocardiography and echocardiography were performed at the referral centre. Blood was collected for haematological and biochemical analysis and cyclosporin concentration. All patients underwent annual review, including estimation of glomerular filtration rate (GFR) to assess the degree of cyclosporin induced nephropathy.^{13 14} Cardiac catheterisation and coronary angiography were undertaken annually from two years after transplant.

STATISTICAL ANALYSIS

Actuarial survival curves were computed by the method of Kaplan and Meier.¹⁵ Actuarial survival rates and rejection and infection rates were expressed as mean (SEM). Height and weight measurements were converted to a SD score using contemporary data for the British population.¹⁶ Mean SD scores were calculated for patients before heart transplantation and at one and two years after transplant. The postoperative mean scores were compared with the preoperative mean scores using the paired Student's *t* test. The pretransplant mean GFR was compared with that after transplant at one and two years using the paired Student's *t* test. A *p* value <0.05 was considered significant.

Results

SURVIVAL

From June 1988 to June 1994, 31 children with dilated cardiomyopathy were accepted for heart transplantation. Eight patients (26%) died before donor organs became available with a mean time to death of 11.6 days. Twenty three patients (74%) had heart transplantation at a mean of 22 days after placement onto the active waiting list (table 1). Median follow up after transplantation was 27 months, with a range of one to 62 months.

The mean (SEM) actuarial survival after transplantation was: 95% (4.87%) at one year, 87% (8.33%) at two years, and 87% (8.33%) at three years after transplant (fig 1). One patient died 45 days after heart transplantation with a postoperative course complicated by recurrent septicaemia (*Escherichia coli*,

Figure 1 Mean (SEM) actuarial survival of patients with dilated cardiomyopathy after heart transplantation. The number of survivors at each year is indicated in parentheses.

Staphylococcus epidermidis, *Streptococcus* spp, *Candida albicans*) and rejection episodes. There was one late death, at 17 months after transplant, due to graft associated coronary artery disease. This patient presented at 14 months after transplant with sudden onset of left hemiparesis; coronary angiography showed an occluded left anterior descending artery with small calibre distal vessels.

One patient underwent retransplantation. This was a 7 year old girl who developed severe graft failure in the immediate postoperative period and required extracorporeal life support. She was successfully retransplanted 12 hours later and remained fit and well five months later. Of the 17 patients who underwent routine review at one year after transplant, including formal assessment of school attendance, school performance and exercise capacity, 16 showed completely normal functioning while one was mildly impaired as a consequence of an early postoperative neurological insult.

REJECTION AND INFECTION

Acute rejection of the allograft was most prominent in the first three postoperative months, thereafter lessening in frequency (table 3). Only two episodes of rejection were documented in separate patients more than 12 months after heart transplantation. In all, we treated 30 episodes of rejection and all responded to intravenous methylprednisolone or augmentation of oral steroids, except one which required a further course of antithymocyte globulin before resolving.

During the study period, 18 episodes of infection were diagnosed. Infection was more prominent in the first three postoperative months (mean 0.652 episodes/patient); thereafter lessening in frequency (mean 0.13 episodes/patient between 3–12 months after transplantation).

Table 3 Cardiac rejection and infection episodes after heart transplantation

Months after transplant (No of patients)	Rejection episodes (mean No/patient)	Infection episodes (mean No/patient)
0–3 (23)	0.957	0.652
3–12 (22)	0.182	0.13

Pathogens isolated on 10 occasions included *E coli*, *Streptococcus* spp, and *Staphylococcus aureus*. The lower respiratory tract was the primary site of infection in five patients, as well as septicaemia (n=2), line sepsis (n=1), and the gastrointestinal tract (n=2).

The majority of clinically diagnosed common viral infections were well tolerated; however major viral infections were infrequent. Two patients developed oral herpes simplex infection which responded to intravenous and oral acyclovir. Three patients seroconverted to Epstein-Barr virus after heart transplantation but have remained well. Six cytomegalovirus negative recipients received hearts from cytomegalovirus positive donors. Three have seroconverted, between two and 22 months after transplantation, but none has shown clinical evidence of cytomegalovirus disease or required gancyclovir treatment. Two patients developed candida septicaemia, one of whom had septicaemia with multiple organisms and died at 45 days after transplant (as described above). The other responded to intravenous amphotericin. One patient received effective prophylactic treatment for a toxoplasma mismatch. None of the patients has developed *P carinii* pneumonitis.

CARDIAC CATHETERISATION AND CORONARY ANGIOGRAPHY

Nine patients have undergone cardiac catheterisation and coronary angiography. Right and left ventricular filling pressures have been normal in all, except one who had coronary artery disease. There was no evidence of venous, pulmonary artery, or supraventricular aortic obstruction. Thirteen coronary angiograms have been performed. Four patients have shown angiographic abnormalities. One patient (15 months after heart transplantation) has an occluded left anterior descending artery with small sized distal vessels. Three patients have evidence of dilatational angiopathy.¹⁷ One patient had dilated proximal and mid-right coronary artery, left anterior descending artery, and left circumflex artery (patient A); the second patient had dilated proximal left anterior descending artery and left circumflex artery (patient B); whereas the third patient had a dilated proximal and mid-right coronary artery (patient C). Dilatation was associated with sluggish contrast washout in all. Dilatational angiopathy was noted in patient A for the first time four years after transplant, and in subsequent angiograms there is evidence of distal vessel disease. The abnormality was first noted in patients B and C at their initial coronary angiograms two years after transplantation. None of these three patients has shown evidence of Kawasaki disease or other systemic polyarteritis syndromes.

GROWTH

Height and weight SD scores are shown in figs 2 and 3 respectively. The mean SD score for height was +0.331 preoperatively, -0.213

at one year, and -0.561 at two years. These differences were not statistically significant ($p=0.56$ and $p=0.63$ respectively). The mean SD score for weight was -1.381 preoperatively, +0.489 at one year, and +0.057 at two years ($p<0.002$).

OTHER ISSUES

Serial GFR measurements have decreased in all survivors. The preoperative mean (SD) GFR was 98.04 (28.56) ml/min/1.73 m² decreasing to 56.48 (11.83) at one year and 45.21 (10.08) at two years. These differences were statistically significant at one and two years ($p<0.002$ and $p<0.005$ respectively), although no patient required dialysis or renal transplantation.

Ten of the 21 survivors (48%) have required long term treatment of hypertension and were controlled on nifedipine (0.5-1.5 mg/kg/day). None has developed accelerated or malignant hypertension.

None of the survivors has developed a neoplasm. The four patients with anthracycline induced cardiomyopathy remain free from recurrence of malignant disease 14, 15, 20, and 34 months after transplant.

One patient did not comply with immunosuppressive treatment because of changes in body habitus including cushingoid features, hypertrichosis, and gingival hypertrophy. He presented in severe cardiac failure at nine months after transplant as a consequence of rejection.

Fine tremor was observed frequently,

Figure 2 Individual SD scores for height preoperatively (0), and at one year (1) and two years (2) after transplant.

Figure 3 Individual SD scores for weight preoperatively (0), and at one year (1) and two years (2) after transplant.

although cyclosporin associated seizures occurred in only four patients (17%). All were receiving continuous intravenous cyclosporin infusions at the time and seizures were controlled with anticonvulsants and conversion to oral cyclosporin.

Discussion

The improved prognosis of heart transplantation in adults, after the introduction of cyclosporin, encouraged transplant centres to embark on paediatric transplantation in the early 1980s.^{18 19} The International Society for Heart and Lung Transplantation reported 1559 heart transplants under the age of 18 years up to 1993.²⁰ The overall actuarial survival was 80% at one year and 75% at three years in the 1–18 year age group. The Stanford group reported a cumulative survival of 84% at one year, 80% at two years, and 77% at five years for heart transplantation in 37 children with dilated cardiomyopathy,⁵ while those at Harefield Hospital reported an actuarial survival in 70 patients with cardiomyopathy of 78% at one year and 69% at four years.²¹ Our five year experience with heart transplantation for children with dilated cardiomyopathy indicates a comparable survival with substantially improved quality of life in the majority of patients.

As expected, acute rejection episodes were more frequent in the first three months after transplantation. In addition, infection was more common in the same period, presumably as a consequence of the augmented immunosuppression administered. We were encouraged to note that common childhood infections were well tolerated as has been the experience in other published reports.^{22–24} Cytomegalovirus mismatching did not lead to the major complications reported elsewhere^{23 25} so we have continued a policy of not matching for cytomegalovirus antibody status and only treating clinically apparent disease.

Graft associated coronary artery disease represents the major cause of cardiac dysfunction and late deaths in patients after heart transplantation. In adults, the incidence has been reported as 2%–24% at one year and 44%–57% at five years.^{26–28} A recent paediatric series reported a prevalence of 83% at five years.²⁹ The unique angiographic hallmark of this disease is diffuse concentric longitudinal narrowing with pruning and obliteration of distal branch vessels, although proximal focal epicardial stenoses may also appear typical of non-transplant coronary artery disease.³⁰

There are limited reports on the angiographic appearance of coronary artery disease in children.^{29 31 32} In our series distal vessel disease was observed in one child and focal proximal in another. However, the predominant abnormality was dilated proximal coronary arteries associated with sluggish washout of contrast (three patients). This has been reported previously in adult heart transplantation patients as 'dilated angiopathy'.¹⁷ Berry *et al* described the histological changes in a child with allograft coronary artery disease

with similar findings, although they did not report angiographic details of their patient.³³ Only one of our patients with dilated angiopathy has left ventricular dysfunction and is symptomatic. Serial angiograms showed this patient has developed distal vessel disease. The remaining three, with dilated angiopathy alone, remain clinically asymptomatic with normal left ventricular function on echocardiography, normal haemodynamics and no evidence of limitation of effort tolerance, exercise induced ischaemia, or arrhythmias. Thus, dilated angiopathy appears to be associated with a better prognosis than the focal proximal and diffuse distal form.

One of our patients did not comply with treatment and ceased taking cyclosporin. Consistent follow up and psychological support is necessary in young patients, particularly for the independence seeking adolescent, who may develop an aversion to the complexities of medical management.

We are encouraged to note that our current triple maintenance immunosuppression regimen, incorporating steroids, has not produced significant growth retardation nor has it been associated with an increased incidence of tumour development. We have avoided using OKT3 for either induction or rescue treatment because of its associated increased incidence of lymphoproliferative disease.³⁴ Newer agents such as FK506 may allow more selective immunosuppression with fewer side effects.³⁵

Optimum timing of heart transplantation in dilated cardiomyopathy is not yet known. There are few reports of the natural history of dilated cardiomyopathy in childhood. Greenwood *et al* reported a death rate of 56% within the first month after diagnosis and 77% within the first year.³⁶ The Mayo clinic reported a 34% mortality rate at five years among 24 patients with dilated cardiomyopathy.³⁷ Age at diagnosis may influence outcome; in two studies, patients presenting before the age of 2 years appeared to have a better prognosis,^{3 38} although this has not been consistently shown.³⁹ The impact has not been evaluated in children of aggressive pharmacological intervention with diuretics, vasodilators titrated to haemodynamic end points, and β adrenergic blocking agents, and orally and intravenously administered inotropic agents.^{40–44} Considerable information is still required to define the history of dilated cardiomyopathy when influenced by intensive medical therapies, to identify the predictors of prognosis, and to determine the appropriate timing of heart transplantation.

Our concerns regarding possible long term morbidity associated with coronary artery disease and immunosuppression has prevented us proceeding to heart transplantation in patients with severe dilated cardiomyopathy who are haemodynamically stable on anti-failure treatment. This is so particularly in those under 2 years of age. There is a constant threat of sudden death or acute deterioration, but on the other hand some patients stabilise and improve.⁴⁵ The dilemma is that there are no definite indicators yet available to forecast

an individual patient's course. Currently, we advocate heart transplantation for dilated cardiomyopathy when the patient is not responding to maximal antifailure treatment, has associated failure to thrive, and a poor quality of life. Despite the morbid events associated with heart transplantation, we have observed improved survival and quality of life in the majority of children who undergo transplantation. Accordingly, we advise early referral for transplantation assessment in children with dilated cardiomyopathy.

We would like to thank other members of the transplant team at the Great Ormond Street Hospital for Children NHS Trust, specifically Mary Goodwin, Ian Martin, Pam O'Shea, Esther Serrano-Ikkos, and Ross Parsons, and Mr John Wallwork (Papworth Hospital, Cambridge) for his enormous contribution in the establishment of our transplant programme. We would also like to thank Professor M Preece (Institute of Child Health, London) for his help with the growth data.

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