The waiting game: bridging to paediatric heart transplantation

Allan P Goldman, Jane Cassidy, Marc de Leval, Simon Haynes, Katherine Brown, Pauline Whitmore, Gordon Cohen, Victor Tsang, Martin Elliott, Anne Davison, Leslie Hamilton, David Bolton, Jo Wray, Asif Hasan, Rosemary Radley-Smith, Duncan Macrae, Jon Smith

Summary

Background Although mechanical circulatory support might not increase the number of adults surviving to transplantation, because of the shortage of donor organs, the situation might be different for children. Our aim was to assess the effect of mechanical assist devices to bridge children with end-stage cardiomyopathy to heart transplantation.

Methods A 5-year retrospective review was undertaken with data from the UK paediatric transplant programme and from bridging to transplant done at two paediatric transplant centres in the UK.

Findings Between Jan 1, 1998 and Dec 31, 2002, 22 children with end-stage cardiomyopathy, median age 5·7 years (range 1·2–17), were supported by a mechanical assist device as a bridge to first heart transplantation, with a 77% survival rate to hospital discharge. Nine were supported by a paracorporeal ventricular assist device, six received transplantation, five survived to discharge (55%), with one late death. 13 were supported by extra-corporeal membrane oxygenation, and 12 were transplanted and survived to discharge (92%) with one late death. With urgent listing, the median waiting time for a heart was 7·5 days (range 1·5–22 days). The correlation between the proportion of patients bridged to transplantation and the proportion of patients dying while on the transplant waiting list was r=–0·93, p=0·02.

Interpretation Our findings lend support to the hypothesis that a national mechanical assist programme to bridge children to transplantation can minimise the number dying while on the heart transplant waiting list. In the context of urgent listing and a short waiting time, extra-corporeal membrane oxygenation seems to provide the safest form of support.

Lancet 2003; **362:** 1967–70
See Commentary page 1948

Great Ormond Street Children's Hospital, Great Ormond Street, London WC1N 3JY, UK (A P Goldman MRCP, Prof M de Leval FRCS, K Brown MRCP, P Whitmore RSCN, V Tsang FRCS, M Elliott MD, J Wray PhD, R Radley-Smith FRCP)**; The Freeman Hospital, High Heaton, Newcastle-upon-Tyne NE7 7DN, UK** (J Cassidy MRCP, S Haynes FRCA, A Davison RN, L Hamilton FRCS, D Bolton FRCA, A Hasan FRCS, J Smith FRCA)**; Royal Brompton and Harefield NHS Trust, London SW3 6NP, UK** (D Macrae FRCA)**; Children's Hospital and Regional Medical Center, Heart Center, Seattle, WA 98115, USA** (G Cohen MD)

Correspondence to: Dr Allan P Goldman, Great Ormond Street Children's Hospital, Great Ormond Street, London WC1N 3JY, UK. (e-mail : goldma1@gosh.nhs.uk)

Introduction

The provision of mechanical circulatory support, although technically successful, might not increase the number of adult patients surviving to transplantation because of the severe shortage of donor organs.[1] This situation could be different in children.

In 1998, we undertook an audit of the UK paediatric transplant data to assess the balance between donor heart availability and paediatric recipient need. This audit showed that during the preceding 2 years, 20 children (19 with end-stage cardiomyopathy) died while on the heart transplant waiting list. These deaths occurred despite 59 donor hearts being offered for transplantation but not used, because no suitable recipient was available (d'Udekem Y, unpublished). We postulated that if all the patients who died while on the waiting list could have been supported on a mechanical device until a suitable heart became available, all but two would have received a transplant within a median time of 2 months.

On the basis of this data, we introduced a paediatric mechanical assist programme in 1998. We used a paediatric paracorporeal ventricular assist device (Medos HIA VAD, Medos, Stolberg, Germany) or extra-corporeal membrane oxygenation (ECMO) to bridge children older than 1 year with end-stage cardiomyopathy (age chosen because of the severe shortage of donor organs for children <1 year) to heart transplantation.

The aim of this study was to review the data for bridging paediatric patients with end-stage cardiomyopathy to heart transplantation at the two UK paediatric transplant/ECMO centres and assess the effect of this strategy on the UK paediatric transplant programme over the past 5 years.

Methods

Bridging to transplant data

We obtained data from the two UK paediatric transplant centres that also serve as supraregional UK paediatric ECMO centres. We reviewed the records of all children with end-stage cardiomyopathy who were supported by a mechanical assist device before first heart transplant at these two centres between Jan 1, 1998 and Dec 31, 2002.

Mechanical support was provided by ventricular assist device or ECMO, dependent on institutional preference and expertise or resource availability. Patients were deemed suitable for mechanical support if they developed signs of a persistent low cardiac output state that was unresponsive to escalating vasoactive drug treatment and when signs and symptoms of end-organ dysfunction were detected (renal, hepatic, or gastrointestinal). Clinically relevant ventricular ectopy associated with increasing inotropic support was also used as an indication for mechanical support because of the risk of ventricular fibrillation and death. Most patients receiving mechanical support, and some who were not, were urgently listed for the next available compatible donor heart (similar

	ECMO (n=13)	VAD (n=9)
Median (IQR) age (years)	10 (1·8–12)	4·9 (1·6–13)*
Median (IQR) patient's weight (kg)	30 (12–25)	18 (12–27)
Median (IQR) time on device (days)	9 (6–10)	6·5 (4–8)
Died before transplant	1	3
Neurological insult or deficit	0	4
Transplanted	12 (92%)	6 (66%)
Survived to discharge	12 (92%)	5 (55%)
Long-term survival	11 (85%)	4 (45%)

*No significant difference in age between the ECMO and VAD group.

Table 1: **Demographics, complications, and outcome of patients**

to United Network of Organ Sharing status 1A). UK paediatric transplant centres can list only one priority patient at a time. We defined survival as survival to transplantation, survival to hospital discharge, and survival to Mar 30, 2003 (ie, a minimum of 3 months after transplantation).

UK paediatric transplant activity

We reviewed the UK National Transplant Database for the total number of paediatric patients listed for transplant, number of transplants undertaken, waiting time for transplantation, and the number of children who died while on the waiting list, over the last 5 years (Jan 1, 1998–Dec 31, 2002).

Statistical analysis

We used Pearson's correlation coefficient to assess the correlation between the number of children with cardiomyopathy who were bridged to transplant over the 5-year period of review, and those who had transplants and also those who died while on the waiting list. An unpaired *t* test was used to compare the age difference between the patients supported on ECMO and ventricular assist device.

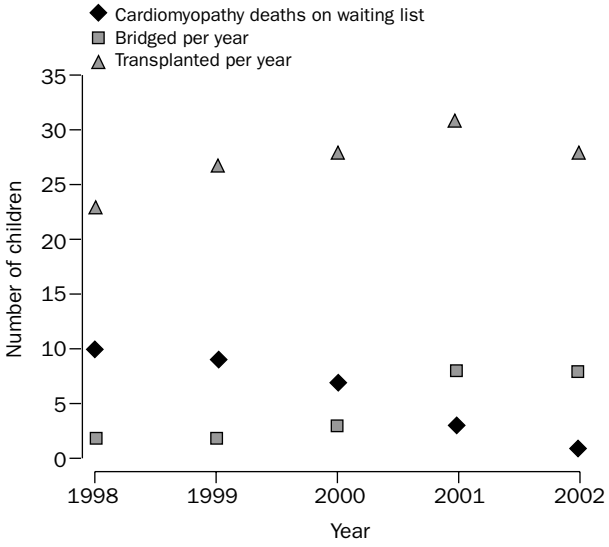
Role of the funding source

The sponsor of the programme had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

22 children with cardiomyopathy (median age 5·7 years, IQR 2–12) were placed on a mechanical device as a bridge to first heart transplant, nine on ventricular assist device and 13 on ECMO. Overall, 18 (82%) of the 22 patients were successfully bridged to transplant, 17 (77%) survived to hospital discharge, and 15 (68%) survived for at least 3 months after transplantation (two late deaths, at 18 months and 4 years after transplantation, respectively).

All 13 of the ECMO patients were supported on venoarterial ECMO, 11 of whom were cannulated via a cut-down through the neck and groin vessels. Nine patients had atrial blade septectomy on ECMO in the cardiac catheter laboratory to offload the left heart. All patients bridged with the Medos ventricular assist device were supported with biventricular devices placed surgically on cardiopulmonary bypass (left and right atrial venous cannulae as well as pulmonary and aortic arterial cannulae).



Relation between number of children with cardiomyopathy bridged to transplant over past 5 years, actual number of paediatric patients transplanted, and number of paediatric patients with cardiomyopathy dying on heart-transplant waiting lists in UK

12 of the 13 patients supported on ECMO received transplants, and survived to discharge. There was one late death, 18 months after transplantation, due to recurrence of the patient's original giant-cell myocarditis.

The median age of the ECMO patients was 10 years (IQR 1·8–12) and median waiting time for a heart was 9 days (6–10) (table 1). One ECMO patient (age 2·5 years) was successfully weaned from support after 5 days without the need for transplantation. This patient, however, needed further ECMO 18 months later, and was successfully transplanted after 22 days of support. In the only patient who died awaiting a heart in this group, ECMO was withdrawn after 21 days of support at the request of the family before an organ became available. This patient was on the active transplant list when ECMO support was stopped.

All patients supported on ECMO were ventilated and received intravenous inotropic support before ECMO (11 [85%] given adrenaline). Five (40%) also needed cardiopulmonary resuscitation before bridging was started, the longest period being 28 min.

Three patients needed re-exploration of the chest for bleeding after ECMO was started. Two had recently undergone mitral-valve annuloplasty in an attempt to delay transplantation, and the third patient, who needed a second run of ECMO, could not be recannulated via the internal jugular or femoral veins, and was thus directly cannulated via the right atrium through a right thoracotomy. There were few complications related to the peripheral cut-down ECMO cannulations. One patient developed severe haemolysis and eight needed renal support (haemofiltration) during ECMO (none long term). All 11 of the long-term ECMO survivors seem to have remained

	Number listed for transplant	Number transplanted	Number died awaiting transplantation	Number bridged to transplant	Median (IQR) waiting time for heart in patients bridged to transplantation (days)	Median (IQR) waiting time to transplantation in all patients transplanted (days)
Age (years)						
0–1	30	12	18	0	..	19·5 (14–37)
>1–4	43	28	15	8	7·7 (7–9)	18 (7–35)
>4–10	37	29	8	5	5 (4–6·5)	15 (7–30)
>10	79	69	10	9	8·8 (6–10)	16 (5–51)

Table 2: **Waiting times for paediatric heart transplantation in UK for 1998–2002**

neurologically intact (functionally normal lives in mainstream school), with a median follow-up of 12·5 months (IQR 10–20). Few of these patients have had head CT, MRI scans, or detailed neurological follow-up, and their long-term neurological outcome thus remains uncertain.

Six of the nine patients supported on the ventricular assist device received transplants, five survived until hospital discharge, and one died 4 years after transplantation because of organ rejection due to non-adherence to immunosuppressive medication. The causes of death were: cerebral haemorrhage (two patients), middle cerebral infarct (one), and rejection and multiple-organ system failure 6 weeks after transplantation (one).

The median age of the patients supported on the ventricular assist device was 4·9 years (1·6–13) and the median waiting time for a heart was 6·5 days (4–8). All were receiving intravenous inotropes (6 [66%] adrenaline), six (66%) were ventilated, and one needed cardiopulmonary resuscitation before insertion of the ventricular assist device.

Six patients needed re-exploration of their chest for bleeding after insertion of the device. Two developed severe haemolysis, and four needed renal support (haemofiltration). Three of the four long-term survivors seem neurologically intact (functionally normal lives in mainstream school), with a median follow-up of 35 months (23–54). None of these children have had a follow-up head CT or MRI scan. One survivor had a posterior fossa bleed after ECMO support subsequent to ventricular assist device bridging and transplantation, and has visual and hearing impairment. During the review period, 189 patients were listed for transplantation, 137 received a heart transplant (106 had end-stage cardiomyopathy, 31 had congenital heart disease) at the UK paediatric transplant centres. At the same time, 257 hearts were available for transplantation from donors younger than 17 years; 120 of these hearts were unused.

The median waiting time for a heart in all the children who had transplantion during this period was 18·0 days (6·0–45·0) compared with 7·5 days (5–9·7) for those bridged to transplant, most of whom (17 of 22) were urgently listed. 15 of the other 115 non-bridged transplanted patients were also urgently listed (table 2).

The correlation of the proportion of patients bridged to transplantation with that of patients dying while on the transplant waiting list was r=–0·93 (p=0·02). For the proportion of patients bridged to transplantation and those who received transplants, the correlation was r=0·95 (p=0·01, figure).

Discussion

Our results support our hypothesis that the introduction of a mechanical assist programme to bridge children to transplantation would lessen the number who die while on the heart transplant waiting list.

A key component of the success of this programme has been the simultaneous implementation of a policy to list as urgent most paediatric patients on mechanical support for the next available matched heart. This policy is in direct contrast to the practice in adults, in which patients are placed on the normal heart transplant waiting list and an implantable device is used to stabilise the patients for long-term periods of months or even years if necessary. This difference in practice is primarily based on the greater shortfall of donor hearts in adults than in children,[1] and the larger variety of ventricular assist devices available for adults than for children. Adults are also frequently supported long term with such devices to improve end-organ function.

When we set out to establish a mechanical support programme in 1998, we anticipated from our audit that we would need to support these patients for extended periods. Unexpectedly, given the change in listing policy, the actual waiting time for donor hearts was much shorter than predicted, being weeks rather than months. Thus, we did not test the true benefit of using the ventricular assist devices for long bridging runs. One possible reason for the better results with ECMO than with the ventricular assist devices might be related to a learning curve with a new mechanical assist device, and the use of left-atrial instead of left-ventricular drainage cannula. Nonetheless, the survival rate until discharge for patients supported on the ventricular assist device in this series (55%) was compatible with other reports in which similar devices were used (36–69%).[2–5]

The high frequency of neurological complications in the ventricular assist devices group was disappointing and probably related at least partly, to clot formation in the pulsatile pump chamber. Although neurological complications have been reported as being lower in patients supported with a centrifugal ventricular assist device pump than in those supported with ECMO,[6,7] clot formation in the pump head and related neurological sequelae have been well described by researchers who used similar paracorporeal devices to those used in this series.[2,3,5] This complication might be lessened by use of a left-ventricular rather than left-atrial drainage cannula and more experience with this device.

The high survival rate we saw for ECMO bridging to transplantation is reinforced by rates from other investigations.[8–11] This finding suggests that ECMO might be the device of choice to bridge paediatric patients to transplantation when the anticipated waiting time for a heart is likely to be short—ie, weeks. The main advantage of such treatment for patients with end-stage cardiomyopathy is that cannulation can be done peripherally via the neck or femoral vessels, and the left heart offloaded by a percutaneous atrial blade septectomy. Use of ECMO avoids the need for a sternotomy and direct placement of cannulae in the heart, thus keeping to a minimum the risk of bleeding and need for chest re-exploration, as seen in our ventricular assist device patients. There is also a substantial experience of ECMO use in children.

The danger of our policy to list as urgent the sickest patients on mechanical support for the next available matched heart is that there could be a harmful knock-on effect on patients who are pushed down the waiting list. Fortunately, these patients did not seem to be negatively affected, and there was a progressive decline in the number of patients dying while on the waiting list over the period of review. No child with cardiomyopathy died on the waiting list in the UK during 2002, except one patient who was taken off ECMO at the parent's request, after 21 days of support. The policy to bridge and list as urgent our sickest patients is also supported by a review of adult cardiac transplantation, in which only the highest-risk adults benefited from cardiac transplantion.[12] We hope that new national urgent listing status will continue to optimise organ use. This approach needs to be continuously monitored.

If the short waiting times for paediatric transplantation we noted represent a cluster effect, they would, of course, not be sustained. If longer waiting times prove to be the norm, introduction of alternative devices capable of providing extended bridging runs will be necessary. Ideally, such devices should be implantable, small enough for the paediatric age range, allow patients to be ambulatory and to need only minimum anticoagulation. Several devices have been used to successfully support adult patients at home for

long periods.[13] Although paracorporeal devices have been used in children for periods of months, the median bridging time to transplantation with these devices has been skewed to the left at around 5–10 days.[2,3,5] Preliminary reports about the next generation of substantially smaller devices classified as miniature implantable centrifugal pumps[14] and axial impeller pumps, such as the Jarvik Screw, are encouraging.[15]

Only patients with end-stage cardiomyopathy were supported on the paracorporeal device, and hence reported in this study. We believed this group to be a homogenous group of patients in whom to initiate a new technique of mechanical assist. These patients generally do better than patients with structural congenital heart disease. A limitation of this study, however, is that we did not have a definitive diagnosis of cardiomyopathy, since few patients had myocardial biopsies because of the risk of this procedure, especially among patients on ECMO. In practice, if a patient had an acute history of cardiac failure that needed mechanical assistance, they were supported on ECMO for several days as a bridge to recovery. If there were no signs from echocardiographical tests or trial of weaning of myocardial recovery, they were listed as urgent for transplantation.

Nine patients outside our study were bridged to recovery on ECMO during the period of this review (most of whom had positive serological findings), with seven (78%) surviving to hospital discharge without transplantation.

In the context of urgent listing, ECMO seems to offer the safest form of short-term bridging to transplantation in children with end-stage cardiomyopathy, yielding excellent survival rates. An optimum device for long-term support as either a bridge to transplantation or recovery, however, does not yet exist in the infant population.

Contributors

J Smith and A Hasan initiated the bridging program at Freeman Hospital and were involved in the care of these children, and contributed throughout inception, development, and writing of this report. S Haynes, D Bolton, and L Hamilton were involved in the care of the children studied, which included discussions about the timing of ventricular assist device placement, technical decisions about the management of the device, and the post-transplant care needed. S Haynes and A Davison were responsible for retrieval and audit of all waiting times for transplantation and organ offers during the study interval for the Newcastle service. S Haynes was involved in discussions during the development of the manuscript. D Macrae contributed to formulation of the research question, data interpretation, and writing and editing drafts of the manuscript. G Cohen contributed to writing and editing of the report, initial conception. G Cohen was responsible for surgical organisation of the ECMO service and undertook most ECMO cannulations and heart transplants. M de Leval and P Whitmore were involved in study design, collation of data, writing of the manuscript. M Elliott contributed to study design, strategy, discussion, and practical aspects of clinical care of the patients. K Brown participated in data collection and writing of the report. A Goldman, J Cassidy, and V Tsang were involved in study design, patients' care, data collation, and writing the report. R Radley-Smith contributed to writing of the report and was involved in patients' care. J Wray contributed to data collection and was involved in patients' care.

Conflict of interest statement

None declared.

Acknowledgments

We are indebted to Yves d'Udekem for his enthusiasm in undertaking the original audit and doing the first VADs at Great Ormond Street Hospital. We thank Deborah Ridout from the Department of Bio-statistics and Epidemiology at the Institute of Child Health, University of London, for her help with the statistical analysis. We thank also the ECMO and transplant teams at Freeman Hospital, Newcastle; Great Ormond Street Hospital, London; and Harefield Hospital, Middlesex, for their dedication and expertise in managing these patients, as well as the National Specialised Commissioning Advisory Group, Department of Health, UK, for funding the transplant and bridging-to-transplant programmes at these centres.

References

1 Hosenpud JD, Bennett LE, Keck BM, Boucek MM, Novick RJ. The Registry of the International Society for Heart and Lung Transplantation: seventeenth official report, 2000. *J Heart Lung Transplant* 2000; **19:** 909–31.

2 Hetzer R, Loebe M, Potapov E, et al. Circulatory support with pneumatic paracorporeal ventricular assist device in infants and children. *Ann Thorac Surg* 1998; **66:** 1498–506.

3 Konertz W, Hotz H, Schneider M, Redlin M, Reul H. Clinical experience with the MEDOS HIA-VAD system in infants and children: a preliminary report. *Ann Thorac Surg* 1997; **63:** 1138–44.

4 Reinhartz O, Keith FM, El-Banayosy A, et al. Multicentre experience with the thoratec ventricular assist device in children and adolescents. *J Heart Lung Transplant* 2001; **20:** 439–48.

5 Reinhartz O, Stiller B, Eilers R, Farrar D. Current clinical status of pulsatile pediatric circulatory support. *ASAIO J* 2002; **48:** 455–59.

6 Duncan B, Hraska V, Jonas R, et al. Mechanical circulatory support in children with cardiac disease. *J Thorac Cardiovasc Surg* 2002; **117:** 529–42.

7 Ibrahim A, Duncan B, Blume E, Jonas R. Long-term follow-up of pediatric cardiac patients requiring mechanical circulatory support. *Ann Thorac Surg* 2000; **69:** 186–92.

8 Kirshbom P, Bridges N, Myung R, Gaynor J, Clark B, Spray T. Use of extracorporeal membrane oxygenation in pediatric thoracic organ transplantation. *J Thorac Cardiovasc Surg* 2002; **123:** 130–06.

9 Nield L, McCrindle W, Bohn D, et al. Outcomes for children with cardiomyopathy awaiting transplantation. *Cardiol Young* 2000; **10:** 358–66.

10 Levi D, Marelli D, Plunkett M, et al. Use of assist devices and ECMO to bridge pediatric patients with cardiomyopathy to transplantation. *J Heart Lung Transplant* 2002; **21:** 760–70.

11 Duncan B, Bohn D, Atz A, French J, Laussen P, Wessel D. Mechanical circulatory support for the treatment of children with acute fulminant myocarditis. *J Thorac Cardiovasc Surg* 2001; **122:** 440–48.

12 Deng M, De Meester Johan, Smits J, Heinecke J, Scheld H. Effect of receiving a heart transplant: analysis of a national cohort entered onto a waiting list, stratified by heart failure severity. *BMJ* 2000; **321:** 540–45.

13 Holman W, Davies J, Rayburn B, et al. Treatment of end-stage heart disease with outpatient ventricular assist devices. *Ann Thorac Surg* 2002; **73:** 1489–94.

14 Daily B, Pettitt T, Sutera S, Pierce W. Pierce-Donachy pediatric VAD. Progress in development. *Ann Thorac Surg* 1996; **61:** 437–43.

15 Frazier OH, Myers TJ, Gregoric ID, et al. Initial clinical experience with the Jarvik 2000 implantable axial flow left ventricular assist system. *Circulation* 2002; **105:** 2855–60.