Changing Patterns of Bridging to Heart Transplantation in Children

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Background: Mechanical support as a bridge to cardiac transplantation in children is an accepted treatment. With improved devices and increasing experience, the length of time that children can be supported has increased. Donor organs remain scarce and there is significant associated morbidity.

Methods: Retrospective review of all children offered mechanical support as a bridge to heart transplant over 10 years in one of the two UK pediatric heart transplant centers. Outcomes during the years 1998 to 2002 were compared with outcomes during the years 2003 to 2007.

Results: Forty children in 41 separate patient episodes received mechanical support as a bridge to transplantation or, in 1 case, to recovery. Survival to transplant or recovery was achieved in 29 of 41 (71%); 26 of 40 children (63%) survived to hospital discharge. Devices used were extracorporeal membrane oxygenation (ECMO), the Medos HIAA, the Berlin Heart (from November 2005) and the Levitronix ventricular assist device (VAD) from 2007. All 3 children supported with the Levitronix survived to transplant (median duration of support 10 days). Ten of 13 children (77%) supported by the Berlin Heart survived to transplant or recovery (median duration of support 44 days). Four of 7 (57%) children supported using the Medos device survived to transplant (median duration of support 7 days). Neurologic events were the most common cause of death in both eras (1998 to 2002 and 2003 to 2008).

Conclusions: Waiting times to pediatric cardiac transplant in the UK have increased. The Berlin Heart allows children to be bridged to transplant over long periods. Neurologic morbidity remains as a major concern. J Heart Lung Transplant 2009;28:249–54. Copyright © 2009 by the International Society for Heart and Lung Transplantation.

Mechanical support as a bridge to pediatric cardiac transplantation improves survival in children with end-stage cardiac failure.[1] However, there is a high risk of device-related complications and waiting times for suitable donor organs are unpredictable. The clinician has to identify those children who could benefit from mechanical cardiac support and then select the appropriate device.

The Freeman Hospital performs 15 to 20 heart transplants each year in children. It is one of the two pediatric cardiac transplantation centers providing a service to the UK and the Republic of Ireland (combined population approximately 64 million). Extracorporeal membrane oxygenation (ECMO) as a bridge to transplantation in children with end-stage heart failure has been offered by this hospital since 1998. The first use of a ventricular assist device (VAD)—the Medos HIAA device, was also in 1998. The Berlin Heart was introduced in November 2005, and the Levitronix VAD in 2007.

We have reviewed our experience with mechanical support to date looking at wait times, changes in the patient population, complications encountered, and survival both to transplant and hospital discharge. At the beginning of this era, support was restricted to those children who were believed to be at imminent risk of death as a consequence of cardiac failure. These children were already ventilated, in multiorgan failure, and on high-dose inotropes. Infants (<1 year of age) were not offered support until 2005. This was because the waiting time for suitable donor organs to become available for infants was believed to be so long that support would be impossible with the available devices at that time. Following the introduction of the Berlin Heart, infants have been offered support.

DEVICE CHOICE AND IMPLANTATION

ECMO involves the use of a modified heart–lung bypass machine, which is used to provide temporary support

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to patients with severe cardiac and or respiratory failure. Cardiac support is provided in the venoarterial mode with cannulation of the patient's right internal jugular vein and common carotid artery. Its advantage is that it can be rapidly deployed, does not require bypass for implantation, and can be used to support patients of all ages and sizes. Its disadvantage is that it is a relatively complex circuit, cannot provide cardiac support alone, and is time-limited.[2]

Three types of VADs were used in our series: two pulsatile paracorporeal (the Medos HIAA device and the Berlin Heart) and one centrifugal pump (the Levitronix). Both the Medos and the Berlin Heart can be used to support patients from infancy to adulthood and to provide either single or biventricular (BiVAD) support.[3,4] The advantage of both is the isolated cardiac support and closed circuit provided by contrast with ECMO. Both are implanted on cardiopulmonary bypass. This is done on moderate hypothermia (30° to 32°C) with circulatory arrest achieved with cold blood cardioplegia. For implantation of a left ventricular assist device (LVAD), the inflow cannula is sited in the apex of the left ventricle and fixed with a series of interrupted pledgeted polypropylene sutures, followed by application of BioGlu. The core of tissue removed from the left ventricle is sent for histologic examination. The other cannulae on the ascending aorta, and for a right ventricular assist device main pulmonary artery and right atrium, are sutured with continuous polypropylene sutures reinforced by interrupted pledgeted polypropylene sutures, followed again by application of BioGlu all around the sutures. The patient is rewarmed and the heart carefully de-aired through the cannulae before the aortic cross-clamp is removed. Cardiopulmonary bypass is discontinued and the Medos or Berlin Heart activated.

By contrast, the Levitronix VAD, as either an LVAD or a BiVAD, can be accomplished in most cases without the use of cardiopulmonary bypass, unless the patient is hemodynamically unstable.[5] This is because the inflow cannula of the LVAD system is sited in the left atrium. All Levitronix cannulae are fixed with purse-string sutures, usually two for each cannula, with four or five pledgets to increase the tightness of tissues around the cannulae. As with the Medos and Berlin Heart, BioGlu is used around all sutures. Although both the Medos and Berlin Heart devices can be used to support all ages, at the time of collating these data, the Levitronix device was only suitable for use in children >40 kg and its use was therefore restricted to children of ≥ 10 years of age.

ANTI-COAGULATION MANAGEMENT

When using ECMO, children were anti-coagulated only with heparin, targeting activated clotting times of 180 to 210 seconds. This was initially the practice followed with the Medos VAD. Activated clotting times were checked hourly. Subsequently, when either the Berlin Heart or the Levitronix devices were employed, both heparin or warfarin and anti-platelet therapy were used. Heparin therapy is targeted to an activated partial thromboplastin time (aPTT) of 70 to 90 seconds, with the aPTT checked every 4 to 6 hours. When the child is extubated and enterally fed, warfarin is introduced to replace heparin, targeting an international normalized ratio (INR) of 2.7 to 3.4. Anti-platelet therapy with aspirin and dipyridamole is continued throughout with the target of $<30\%$ aggregation on platelet function testing.

Children on mechanical support are urgently listed for cardiac transplantation. ABO blood group mismatch transplantation has been offered since 2000 in the presence of low blood group antibody titers in the recipient.

METHODS

A retrospective review of all children offered mechanical support as a bridge to cardiac transplantation was carried out examining data from January 1998 to December 2007. The Mann–Whitney *U*-test was used for comparisons of continuous data, and the chi-square test for comparisons of categorical data. The need for review by the institutional review board was not required by our institution. All parents consented to inclusion of their child's data.

RESULTS

Over 10 years, 40 children (41 episodes of support) with end-stage heart failure were offered mechanical support as a bridge to transplant (BTT). Of the 40 children, there were 22 girls and 18 boys. The median age at presentation was 36 months (range 1 to 191 months). Dilated cardiomyopathy was the most common diagnosis, present in 25 patients, of whom 19 (76%) underwent successful BTT. Nine children had end-stage heart failure as a result of congenital heart disease (6 with biventricular physiology, 3 with univentricular); 6 of the 9 (67%) had successful BTT. The remaining diagnoses were anthracycline-induced cardiomyopathy (2 patients), myocarditis (2 patients), neonatal myocardial infarct (1 patient), post-transplant infarct requiring a second episode of support (1 patient) and restrictive cardiomyopathy (1 patient).

Data were analyzed as a whole and then outcomes from the two separate eras, 1998 to 2002 and 2003 to 2007, were compared.

One child with acute myocarditis recovered and was successfully explanted from his VAD after 120 days of support. One child was bridged to a first transplant, but then collapsed 14 days after transplantation, sustaining a large myocardial infarct. He was massaged onto

Table 1. Results by Support Mode

Mode of support	*N*	Median age in months (range)[a]	Median length of support in days (range)[b]	Number surviving to transplant (%)[c]	Number surviving to hospital discharge (%)[d]
ECMO	18	60 (1–191)	7 (1–23)	12 (67)	10 (55)
Berlin Heart	13	23 (2.5–190)	44 (7–150)	10 (77)	9 (69)
Medos	7	45 (22–78)	7 (3–13)	4 (57)	3 (42)
Levitronix	3	167 (130–170)	10 (5–16)	3 (100)	3 (100)

[a]No significant difference in ages between the patient groups receiving different modes of support.

[b]Length of support when the Berlin Heart was used was significantly ($p < 0.01$) greater when compared with the other modes.

[c]No significant difference in proportions surviving to transplant when comparing modes of support.

[d]A decreased proportion of ECMO group patients survived to hospital discharge ($p < 0.05$) compared with all other patients combined. An increased proportion of Berlin Heart group patients survived to hospital discharge ($p < 0.01$) compared with all other patients combined. There was no significant difference between ECMO and Berlin Heart groups in survival to hospital discharge.

ECMO; he was neurologically intact and was bridged to a second transplant. Overall survival to transplant or recovery was thus 29 of 41 (71%) episodes of support, or 28 of 40 (70%) patients. Survival to hospital discharge was 26 of 41 (63%) episodes of support, or 25 of 40 (63%) patients.

All patients supported with the Medos device had BiVAD support (Tables 1 and 2). Of the 13 patients supported by the Berlin Heart, 8 had a BiVAD inserted initially, 2 were initially LVAD only but were converted to BiVAD support, and 3 were supported throughout with an LVAD alone.

Twenty-one patients (51%) had had a cardiac arrest prior to institution of support. Nine of the 21 died as compared with 6 of 19 children who did not have a cardiac arrest (not statistically significant).

Of the 15 deaths, 9 (60%) occurred on mechanical support before transplantation. Four of these patients were on ECMO, 3 on the Medos device and 2 on the Berlin Heart. Two deaths were the result of air embolism at reoperation and 4 (27%) occurred after transplant.

Causes of death on support were neurologic complications (4 patients), sepsis (2 patients), ischemic bowel (1 patient), intractable multiorgan failure (1 patient), and 1 occurred after withdrawal of mechanical support at the parents' request.

Two of the deaths after transplant were the result of neurologic insult, including 1 as the result of acute rejection 6 weeks after transplant and 1 secondary to ischemic bowel.

Nineteen patients had neurologic complications, with 13 of these occurring while the child was on mechanical cardiac support. One patient had a cerebral hemorrhage, 1 had a combination of cerebral hemorrhage and infarct, and 17 had sustained cerebral infarcts.

Of the aforementioned 13 children, 5 were supported with ECMO, 4 with the Medos, 3 with the Berlin Heart and 1 with the Levitronix (Table 3). Six children had a neurologic event outside the period of mechanical support. One child, known to have a large clot present in the left ventricular cavity, had a thromboembolic stroke during the transplant procedure. Two further children had events occurring at the time of transplant (1 cerebral hemorrhage, 1 cerebral venous infarction), 2 sustained air embolism at reoperation, and 1 had a stroke several days after transplant, temporally related to removal of a left atrial pressure monitoring line.

Of the children who had a neurologic insult, 10 of 19 (53%) survived to hospital discharge as opposed to 16 of 21 (76%) of those who did not (statistically non-significant). Six of the 10 children who survived after a neurologic event have significant permanent neurologic sequelae. The median age of the 13 children who had a neurologic event while on support was 34 months (range 2.5 to 167 months). There was a statistically non-significant trend toward fewer neurologic incidents in patients >5 years of age. The median length of support in children with neurologic insult was 11 days

Table 2. Outcome by Age

Age in months	Number	Number (%) surviving to hospital discharge[a]
0–12	6	4 (67)
13–60	19	10 (53)
>60	16	12 (75)

[a]No significant difference between age groups in proportions surviving to hospital discharge.

Table 3. Morbidity

	Number (% of all patients)
Renal failure requiring dialysis	16 (39)
Culture proven sepsis	11 (27)
Ventilator dependency throughout support period	30 (73)
Other organ failure	5 (12)
Neurological insult during support period	13 (32)

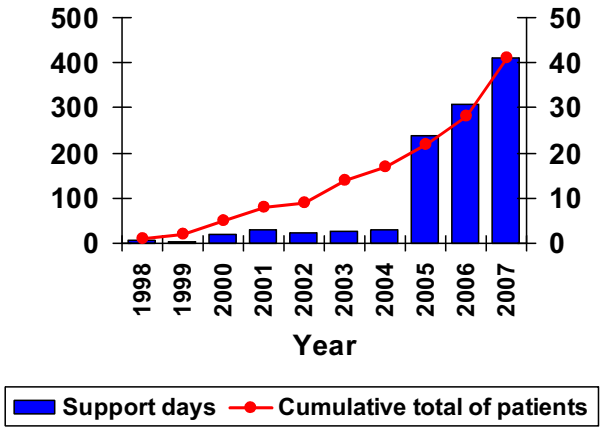

Figure 1. Days of mechanical support offered per year, 1998 to 2007.

(range 1 to 119 days). All of the events occurred within the first 3 weeks of support.

The data were also examined in two cohorts: 1998 to 2002 and 2003 to 2007. In the first era the only modes of support available were ECMO and the Medos HIAA VAD. The second cohort included patients supported with both the Berlin Heart and the Levitronix VAD.

The increased workload in terms of the number of support days per year with the advent of the Berlin Heart and the ability to offer longer runs of support is shown in Figure 1 and Table 4.

DISCUSSION

When mechanical support as a BTT was first introduced it was offered as a desperate therapy in children with multiorgan failure, in whom death was imminent. Some children survived; allied with the recognition that each year hearts from young donors were unused, this led to the development of the UK BTT program, the results of which were published in 2003.[1] In 2003, our strategy seemed clear. We had good results with ECMO and a policy of urgent listing for transplant gave a relatively short median wait time of 7.5 days. Anecdotal reports of the USA experience with ECMO differed, but in the light of these results the UK policy was defined as offering ECMO as a BTT.

Waiting times subsequently lengthened—the median is now 14 days (from the initiation on support) compared with the 7.5 days seen during our first 5-year epoch. Not surprisingly, with longer wait times, the ECMO "honeymoon" ended and at the same time the results from the Berlin Heart Institute[6] were such that the use of VADs had to be reconsidered.

The use of a paracorporeal, closed circuit ventricular assist device has allowed us to significantly extend the support time. This has influenced our policy in smaller children: among infants, in whom we would expect to wait longer for a suitable donor organ, mechanical support to the point of transplant is now a more realistic option. Knowing that there is a device available with good results for longer periods of time has meant that we no longer wait for children to be ventilated with multiorgan failure before mechanical support is considered. This is illustrated by the fact that, in our later cohort of patients, a trend can be seen toward fewer children requiring renal replacement therapy and that 40% were extubated and nursed in a lower dependency environment. None of the children supported either with ECMO alone or the Medos HIAA VAD could be extubated.

Although we believe that the strategy of mechanical support offers children with end-stage heart failure a lifeline, it has associated risks. Almost half of our patients had a neurologic event at some point in their

Table 4. Outcome by Era

	Group A: 1998–2002	Group B: 2003–2007	Comparison Group A v Group B
Number of patients	9	32	
Devices used:			
ECMO	4	14	
Medos	5	2	
Berlin Heart	0	13	
Levitronix	0	3	
Survival to hospital discharge (%)	5 (55)	21 (66)	NS
Median age (range) in months	34 (14–78)	45 (1–191)	NS
Median length of support (range) in days	8 (2–23)	14 (1–150)	$P < 0.01$
Total support days in era	102	995	
Cardiac arrest (number surviving)	5 (1)	16 (11)	$0.05 < P < 0.1$
Renal replacement therapy (%)	6 (67)	10 (32)	$0.05 < P < 0.1$
Ventilatory support throughout (%)	9 (100)	19 (59)	$P < 0.01$
Sepsis (%)	3 (33)	7 (22)	NS
Low dependency care (%)	0 (0)	8 (25)	$0.05 < P < 0.1$
Commonest cause of death (% of total deaths)	Neurological (50)	Neurological (64)	

clinical course, with 13 of 19 occurring during support. This means that a child offered mechanical support as a BTT or recovery has 33% chance of a significant neurologic event associated with the likelihood of permanent disability. A similar neurologic morbidity rate has been noted by the Stanford group[7] and also by the Arizona group, who reported survival of 70% in 10 children supported to either transplant or recovery with pulsatile VADs but with 4 (40%) children suffering thromboembolic neurologic complications.[8]

In our patients there was a trend toward a higher frequency of neurologic events occurring in patients supported with ECMO or the Medos device, and a lower frequency in patients supported by the Berlin Heart and Levitronix devices. This may reflect more effective anti-coagulation rather than a feature of the devices; a combination of anti-platelet therapy and more attentive monitoring of heparin dose by the aPTT rather than whole blood activated clotting times was used latterly rather than reliance on heparin alone. However, neurologic injury remains a problem.

All neurologic events occurred at an early stage of mechanical support, suggesting that the blood/biomaterial interactions differ with the passage of time. The ideal biocompatible surface for blood is functioning native endothelium. To date, it has not been possible to create an endothelial layer on bioprosthetic surfaces. This means that the only options for preventing unwanted thrombogenesis are: the avoidance of excessively thrombogenic materials in the biomaterials used; optimal pump design—avoiding turbulent flow whenever possible; and pharmacologic anti-coagulation of the patient's blood. Slaughter et al suggested that the hypercoagulability and fibrinolytic state seen on implantation of axial flow LVADs wanes with time[9]; this suggests that there is an initial activation of the patient's coagulation cascade caused by implantation of the device. It is also known that blood protein interactions with a biomaterial surface are dynamic, changing as time passes. A biomaterial surface is populated with different proteins over time after initial exposure to blood. This change is termed the Vroman effect.[10] If the protein adsorbed is biologically active (e.g., an enzyme or molecule, which can trigger surface receptors such as glycoprotein IIb/IIIa in platelets) the results are clinically important. Other proteins such as fibronectin or fibrinogen can also activate the immune system.

The patient's genetic make up also influences the likelihood of unwanted thrombus formation. Popatov et al[11] described increased bleeding and response to aspirin in VAD patients who possess the A1/A1 genotype for the GP IIb/IIIa receptor.

In the last year the introduction of the Levitronix VAD has offered another potential option. As a nonpulsatile paracorporeal VAD, it is licensed to provide up to 30 days of support. An advantage is that it can be inserted without cardiopulmonary bypass and thus be deployed rapidly. It is currently only available for children >10 years of age, although a smaller device is in development. It is an alternative to ECMO while offering the VAD benefits of early extubation. In older children, where in the UK one would expect to obtain a suitable donor heart offer within days, it is particularly suitable. Concerns regarding thromboembolic neurologic events are possibly heightened by atrial rather than apical cannulation, meaning that the left ventricle can potentially become filled with clot.

Our results in the last few years have led us to develop an algorithm for the management of children with end-stage heart failure who require mechanical support as a bridge to transplant or recovery. In the event of a cardiac arrest, ECMO provides immediate resuscitation at all ages. Once stabilized on ECMO, appraisal is made of the child's overall condition, confirmation of suitability for transplantation, and whether weaning is possible or the ECMO should be regarded as a "bridge to a bridge." If the child has not sustained a cardiac arrest but is thought to be deteriorating despite maximal medical support and no contraindications to transplant are present, then the decision regarding the mode of support is influenced by the likely wait time for availability of a donor organ. In a young (<10 years) child, the decision will be implantation of a Berlin Heart. This is based on their likely wait time—the median length of support in children <5 years in our series was 14 days (range 2 to 150 days). In an older child with no confounding factors, such as a high panel-reactive antibody level, the wait time is considerably shorter—the median length of support in children >5 years was found to be 6 days (range 1 to 82 days). The Levitronix VAD would be our option of choice in those circumstances as a "short-term" device, which can be placed off bypass. This policy is facilitated by the UK urgent listing status given to any child on mechanical support. If, at any age, recovery of function is anticipated over a prolonged period, then the Berlin Heart would be utilized.

During the last 10 years, wait times for donor hearts have lengthened; concurrently, experience with mechanical cardiac support has increased. Given the ongoing developments, and in particular the NIH trials currently in progress,[12] this is a field that will continue to develop and change. A cautionary note is the learning curve associated with any device. It is essential that lessons learned are shared. Berlin Heart survival is now 65% worldwide, but survival at the Berlin Heart Institute is >80%,[13] a testament to their experience in device manipulation and coagulation management.

As mortality falls, preventing morbidity becomes ever more essential. In addition to device design, it is critical that we find the correct balance between achieving hemostasis and preventing thromboembolism.

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