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A longer waiting game: Bridging children to heart transplant with the Berlin Heart EXCOR device—the United Kingdom experience

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mechanical circulatory support;
end stage heart failure;
heart transplant;
ventricular assist device;
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BACKGROUND: Mechanical circulatory support (MCS) is used to support children with end-stage heart failure to heart transplant.

METHODS: This was a retrospective cohort study of 7 years' experience with the Berlin Heart (BH) EXCOR (Berlin Heart AG, Berlin Germany) paracorporeal ventricular assist device (VAD) in 2 United Kingdom (UK) pediatric heart transplant centers and the effect of this program on the UK pediatric heart transplant service.

RESULTS: Of 102 children who received BH support, 84% survived to transplant or BH explant and 81% survived to discharge. Neither age nor duration of support influenced outcome. Stroke, ongoing requirement for ventilation while on BH, and diagnosis other than dilated cardiomyopathy were the only independent mortality risk factors. Children who weighed < 20 kg had significantly ($p = 0.03$) longer support times than bigger children. The number of children treated with a BH increased over time ($p = 0.01$). Currently $> 50\%$ of pediatric heart transplants are bridged with a BH; however, pediatric transplants per year have not increased significantly ($p = 0.07$)

CONCLUSIONS: BH use in the UK has allowed significant increases in the number of children with end-stage heart failure who can be successfully bridged to transplant and the length of time they can be supported. The total number of transplants has not increased.

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Mechanical circulatory support (MCS) as a bridge to heart transplantation (BTT) in children has been used in the United Kingdom (UK) since 1997 by the 2 UK pediatric heart transplant centers—Freeman Hospital in Newcastle and Great Ormond Street Hospital for Children in London. This was initially with extracorporeal membrane oxygenation (ECMO), and good results were reported in older children.[1] However, given the waiting times and limited donor organ availability, infants were not offered MCS as BTT at that time. Longer waiting times led to a requirement for devices capable of offering prolonged support for children of all ages.[2,3] For most children, transplantation is the only successful exit, placing demands on a limited donor organ resource.

Since 1997, the 2 UK pediatric heart transplant centers have worked collaboratively as part of the UK pediatric heart failure MCS program to deliver a national service with

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regular audit and benchmarking. Management protocols are unit-based but fundamentally similar. Patients are distributed between the 2 centers according to bed availability and geographic location, with agreement from the 2 centers required for urgent transplant listing status.

We aimed to (1) review the UK experience with the Berlin Heart (BH) EXCOR (Berlin Heart AG, Berlin Germany) in outcomes, device-related complications, and mortality risk factors and (2) examine the BH effect on UK pediatric heart transplants.

Material and methods

This was a retrospective cohort study performed between December 2004 and December 2011 of all children listed for heart transplantation requiring BH EXCOR ventricular assist device (VAD) implantation in the 2 UK pediatric heart transplant centers. A waiver of informed consent was granted at both institutions. Data collected included demographics, diagnosis, mode of support (left VAD [LVAD], biventricular assist device (BiVAD), or univentricular assist device), duration of support, and complications (neurologic, end-organ dysfunction, resternotomy for bleeding, and other hemorrhagic or thromboembolic complications). Organ dysfunction was classified using International Pediatric Sepsis and Organ Dysfunction Consensus Conference criteria.[4] Stroke was defined using the World Health Organization definition.[5] All children with clinical stigmata of stroke received neuroimaging and the infarct was then classified as thromboembolic or hemorrhagic. A myocardial biopsy was performed in all children at the time of BH implantation.

Outcomes assessment

Primary outcomes assessed were competing outcomes leading to BH explantation (death, heart transplantation, or recovery) and in-hospital mortality. Secondary outcomes were BH-related complications: stroke, other thromboembolic events, bleeding requiring resternotomy, and sepsis. The decision on explantation suitability was taken based on the child's underlying condition and his or her clinical and echocardiographic response to stress testing over 90 minutes with the VAD paused. If hemodynamic stability was maintained with a fractional shortening of greater than 25% and a normal dobutamine response was demonstrated, the VAD was explanted.

Additional data from National Health Service Blood and Transplant Authority (NHS BT) included the number of children listed for heart transplantation, total pediatric heart transplants, and number of deaths occurring while listed for heart transplantation during the financial years of the study period (April 2004–March 2011).

Transplant donors are drawn from the whole of the UK and the Republic of Ireland as well as from mainland Europe, with mainland Europe donor hearts being offered to UK recipients if no local recipient is available.

Data analysis

Continuous data are presented as mean ± standard deviation for normally distributed data or median (range) otherwise. Nominal or categoric data are presented as number (%). For between-group comparisons of continuous data, such as age at VAD implantation, weight, or duration of VAD support, the Wilcoxon rank sum or Kruskal-Wallis tests were used given the skewed distribution of the data. Nominal or categoric variables were compared using a chi-square test or Fisher's exact test, when appropriate. Logistic regression was performed to estimate the odd ratio and confidence intervals for dichotomous outcomes. The 3 immediate outcomes of VAD implantation—in-hospital mortality, heart transplantation, and VAD explantation—were modeled as time-dependent competing events, and the cumulative incidence of each event was estimated using previously described methods.[6]

Tests for trends in the NHS BT data over time were performed using a non-parametric test for trend across ordered groups. These analyses were performed using STATA 9.2 software (StataCorp LP, College Station, TX) and a p -value < 0.05 was considered significant.

Results

Patient characteristics

During the study period, 102 children required BH support for a total of 5,247 days of support. Patient characteristics before BH implantation are given in Table 1. At the time of BH implantation, 47 children (46.1%) weighed ≤ 10 kg, and 93.1% of children were receiving mechanical ventilation. All were receiving multiple inotropes. Before BH implantation, 1 in 4 children had sustained at least 1 cardiac arrest and 25 (24.5%) required ECMO support. Dilated

Table 1 Patient Characteristics

Variables	No. (%) or median (range) ($N = 102$)
Pre-implantation	
Female	59 (57.8)
Age, months (months–years)	30.5 (0–16.9)
Weight, kg	11.6 (3–90)
Diagnosis	
Dilated or anthracycline cardiomyopathy	68 (66.7)
Myocarditis	10 (9.8)
Congenital heart disease	13 (12.7)
Other[a]	11 (10.8)
Cardiac arrest before VAD	24 (23.5)
Mechanical ventilation	95 (93)
Extracorporeal membrane oxygenation	25 (24.5)
Post-implantation	
Mechanical ventilation throughout VAD support	28 (27.5)
Cerebrovascular accident on VAD support	26 (25.5)
Renal failure	21 (20.6)
Any organ dysfunction	42 (40.2)
Biventricular assist device	38 (37.3)
Sepsis	31 (29.4)
Survival to transplant or explant	86 (84.3)

VAD, ventricular assist device.

[a]Restrictive cardiomyopathy ($n = 3$), hypertrophic cardiomyopathy ($n = 2$), arrhythmogenic cardiomyopathy ($n = 1$), Kawasaki disease ($n = 1$), metabolic cardiomyopathy ($n = 1$), hypertensive cardiomyopathy ($n = 1$), graft failure ($n = 1$), rejection ($n = 1$).

cardiomyopathy was the commonest indication for implantation in 68 patients (66.7%). Support was with an LVAD in 59 children (57.8%), a BiVAD in 38 (37.3%), and a univentricular VAD in 5 (4.9%) with single-ventricle physiology.

The overall the median support time was 39 days (range, 1–252 days). This was longer in children who weighed ≤ 20 kg compared with those weighing $>$ 20 kg (43 days [range, 1–252 days] vs 24 days [range, 1–168 days], $p = 0.033$; Figure 1). No significant differences were noted in the length of VAD support by year during the study period ($p = 0.15$). Figure 2 shows the growth of the UK pediatric VAD program.

Outcomes

Of the 102 children in the study, 74 (72.5%) survived to transplantation, and 12 (11.8%) demonstrated sufficient recovery of myocardial function for explantation. Overall survival to heart transplant or BH explantation was 84.3%, with an 81.4% survival to discharge. Competing outcomes of support over time are shown in Figure 3.

Risk factors for death

Associations between patient characteristics and mortality are listed in Table 2. Variability in survival was noted between diagnostic groups (64%–92%, $p = 0.02$). The diagnosis of DCM had the best survival compared with other diagnostic groups (odds ratio, 0.23; 95% confidence interval, 0.076–0.71). Children with congenital heart disease had the lowest survival (69%) of any individual group. This group included 5 children with single-ventricle physiology and ventricular failure after a Glenn shunt. Three survived to transplantation, but of note, all had short support times of 3 to 7 days. Two died of multiorgan failure after 16 and 61 days of support, respectively. The other significant variables identified as mortality risk factors on univariate analysis

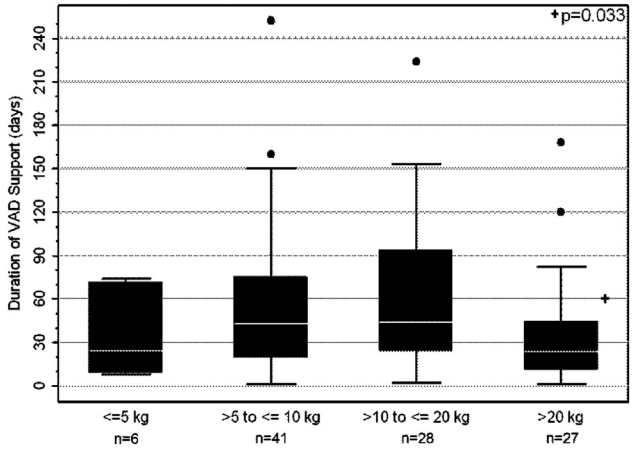

Figure 1 Duration of Berlin Heart support by patient weight. The horizontal line in the middle of each box indicates the median; the top and bottom borders of the box mark the 75th and 25th percentiles, respectively; and the whiskers mark the 90th and 10th percentiles.

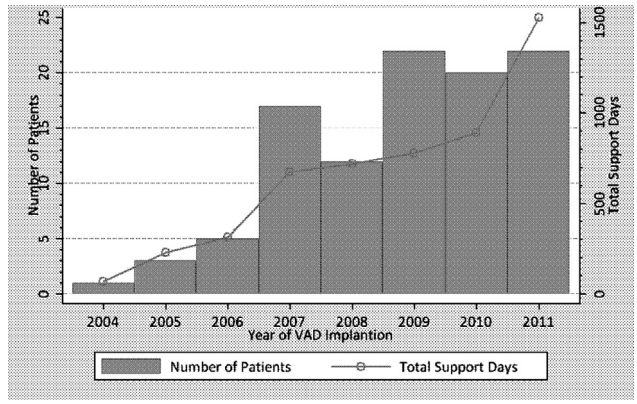

Figure 2 Growth of the United Kingdom Berlin Heart program.

were stroke and a requirement for ongoing ventilatory support during VAD support (Table 2). There was no association between age and mortality ($p = 0.7$) and, specifically, no significant difference between infants and older children ($p = 0.99$).

Causes of death

Of the 16 children who died, the primary cause in 7 was multiorgan failure, followed by catastrophic strokes in 6. Two children died of overwhelming sepsis and 1 of massive air embolism at resternotomy with an infective aortic pseudoaneurysm. Most deaths (68.8%) occurred within 1 month of support (Figure 3).

Morbidity

Twenty-six children (25.4%) had a stroke while receiving BH support; of these, 23 were thromboembolic and 3 were hemorrhagic. Six children died while on support and a further 2 died of their neurologic injury after transplant or BH explant. Although thromboembolic strokes occurred

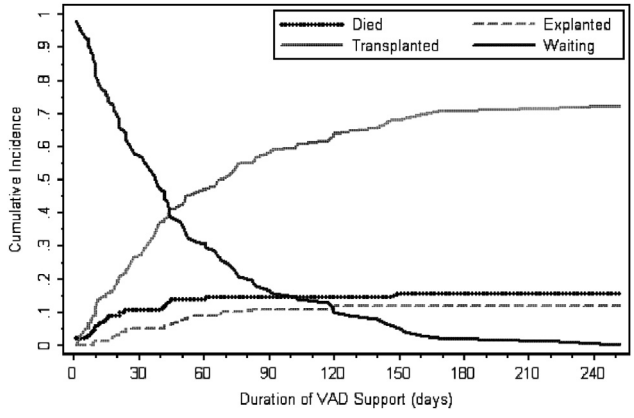

Figure 3 Competing outcomes of Berlin Heart support, which were mutually exclusive, were (1) death occurring while on ventricular assist device support, (2) heart transplantation, (3) explantation after weaning from ventricular assist device, and (4) children waiting on ventricular assist device who had not had any of the other outcomes.

Table 2 Risk Factors for Death on Support

Variables[a]	Survived ($n = 86$)	Died ($n = 16$)	p-value
Pre-implantation			
Age, months (months–years)	27 (1–16.9)	30 (0–15.7)	0.7
Diagnosis			0.02
Dilated cardiomyopathy	62 (91.2)	6 (8.8)	
Congenital heart disease	9 (69.2)	4 (30.8)	
Myocarditis	8 (80.0)	2 (20.0)	
Other[b]	7 (63.6)	4 (36.4)	
Extracorporeal membrane oxygenation	20 (23.2)	5 (31.25)	0.53
Cardiac arrest pre-VAD	18 (20.9)	6 (37.5)	0.15
Post-implantation			
Mechanical ventilation throughout VAD support	17 (17.4)	11 (68.8)	<0.001
Cerebrovascular accident on VAD support	18 (20.9)	8 (50.0)	0.03
VAD support, days	41 (2–252)	15.5 (1–150)	0.01
Renal failure	15 (17.4)	6 (37.5)	0.09
Any organ dysfunction	32 (37.2)	10 (62.5)	0.09
Biventricular assist device	30 (34.9)	8 (50.0)	0.25
Sepsis	24 (27.9)	7 (43.8)	0.21

VAD, ventricular assist device.
[a]Categoric data are presented as number (%) and continuous data as median (range).
[b]Restrictive cardiomyopathy ($n = 3$), hypertrophic cardiomyopathy ($n = 2$), arrhythmogenic cardiomyopathy ($n = 1$), Kawasaki disease ($n = 1$), metabolic cardiomyopathy ($n = 1$), hypertensive cardiomyopathy ($n = 1$), graft failure ($n = 1$), rejection ($n = 1$).

throughout a child's BH course, all lethal strokes were within the first 6 weeks.

One child required small bowel resection as a result of a thromboembolic mesenteric infarct. Thirty-two children (31.4%) required re-exploration for mediastinal bleeding—all within the first month of support. Five children (4.9%) had significant gastrointestinal bleeding. Two had hepatic bleeding related to interventions (1 after insertion of a transhepatic Hickman line and 1 after a right-sided chest drain insertion).

At least one culture-proven episode of sepsis occurred in 31 children (30.4%), most commonly infections were related to a Hickman line, followed by cannula site infections. Twenty-eight children (27.5%) required ongoing ventilation, with an average time of ventilation of 21 days. This was not associated with infancy or stroke. These children were, however, more likely to have had a cardiac arrest before BH implantation ($p = 0.04$) and to require BiVAD support ($p = 0.04$)

Overall morbidity rates were high, and only 37 children (36%) survived to transplant or explant without at least

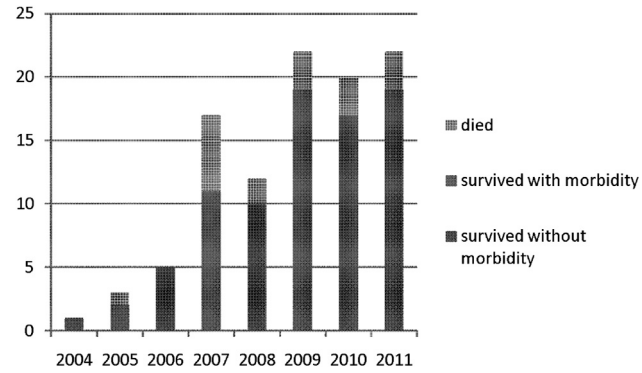

Figure 4 Morbidity while being supported by the Berlin Heart device.

1 morbidity event. This frequency did not change with time (Figure 4).

Explantation

Recovery of cardiac function allowed BH explantation after 12 episodes of support in 11 children. Diagnoses in these children included DCM in 5, myocarditis in 4, and graft failure, congenital heart disease, and restrictive cardiomyopathy in 1 child each. Explantation was done on cardiopulmonary bypass with fibrillation of the heart. The apex was oversewn with pledgetted sutures after careful removal of clots and peel surrounding the apical cannula. The aorta was repaired using the Dacron (DuPont, Wilmington, DE) cuff of the aortic cannula in those patients where a Dacron tube graft was used as an extension of the aortic cannula and using a pericardial patch in those patients where no extension was used.

Median length of support before explantation was 44 days (range, 9–120 days). Two patients died, and 3 subsequently received a transplant. The 2 deaths after explantation were caused by multiorgan failure in 1 patient and multiple thromboembolic strokes sustained during BH support in the second.

One child with relapsing familial DCM was supported 3 times with a BH in this 7-year period. She was explanted on 2 occasions (after 50 and 16 days of support) and was discharged home. On the third occasion after 28 days of support, she underwent a successful transplant.

Thus 6 of 11 children whose BH was explanted survived without transplant, and 4 of these made a complete recovery. One child has significant neurodevelopmental sequelae consequent to multiple thromboembolic strokes, and 1 child supported for graft failure after heart transplant was left with significant morbidity, including bilateral above knee amputations and renal failure, resulting from severe low cardiac output state before BH support.

Transplantation background

From 2005 to 2011, 226 children received transplants in the UK. Data from NHS BT show that the number of pediatric transplants has remained at between 26 and 40 per year since 2004.[7] During the same period, the proportion of children who

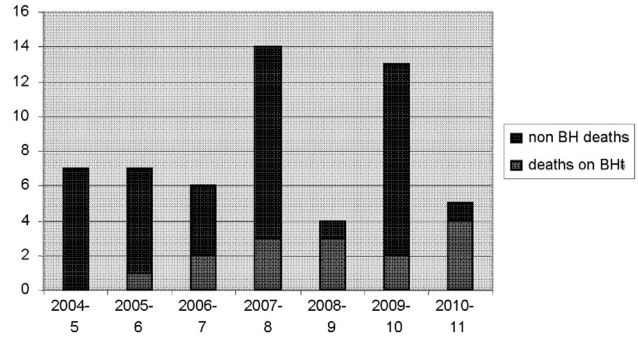

Figure 5 Deaths on the United Kingdom pediatric heart transplant waiting list.

received transplants who also received MCS as a BTT has increased from 12.3% to 59% ($p = 0.025$; Figure 6).

Between April 2004 and March 2011, 56 children died on the transplant waiting list[7]; of these, 16 (29%) died while supported with the BH (Figure 5), and a further 6 were receiving other forms of MCS. Overall, 10% to 30% of children listed in this time period died per year on the waiting list (Figure 6). Median waiting time for non-urgently listed children was 93 days (data to March 2009) vs a median length of 39 days in the BH group.

Discussion

Between 1998 and 2003, MCS as a BTT in the UK was used in only 22 children. Support in 9 of these was by a VAD and the remaining 13 by ECMO. With urgent listing, the median waiting time in this era was 7 days, with the longest 22 days.[1] The UK BH program has allowed significant increases in both number of children BTT and the length of time they can be supported. As the only realistic device currently available for infant support, the BH has allowed extension of the program to the infant population, with no difference in mortality or morbidity compared with older children and potentially better long-term survival.[8] The initial UK experience with the use of MCS before 2003 suggested that its use led to a reduction in the numbers of children dying while waiting for a heart transplant.[1] This has not been sustained (Figures 5 and 6). Given the static transplant rate and the gradual increase in transplant

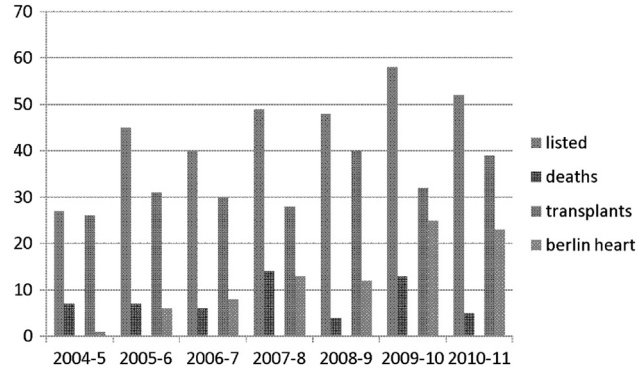

Figure 6 Total number of children listed for cardiac transplant per year vs Berlin Heart numbers, transplants, and deaths on the waiting list (financial year data).

candidates, it is no surprise that the median length of support is considerably longer compared with a waiting time of 7.5 days in the 1998 to 2003 era.[1]

Competing outcome analysis shows that by 5 months of support, virtually all children have received a transplant, the device has been explanted, or they have died on support. This is similar to North American data.[9]

Children offered support were in end-stage cardiac failure with end-organ dysfunction requiring multiple inotropes. The acuity of these presentations did not change significantly with time because most children were referred to the transplant units for consideration of MCS from their regional cardiology centers. Nevertheless, 84% survived to transplant or explant, reflecting the concentration in MCS expertise between the 2 centers. Surprisingly, multiple factors previously suggested as mortality predictors, including infancy, use of ECMO pre-VAD implantation, cardiac arrest pre-VAD, BiVAD support, and congenital heart disease etiology, were not significant.[10–13] The only independent risk factors for death were stroke and ongoing ventilation while on BH support. The chance of a successful outcome was highest in those with DCM.

We did not demonstrate a statistically significant increase in mortality with renal failure, which may reflect the smaller numbers in this study compared with the North American experience.[13] Although the patient population and waiting times were similar in both studies, the UK patients were split equally between the 2 institutions compared with the 47 centers in North America, which may also account for some of the differences.

BH use is a resource-intensive therapy with significant morbidity: 25% of children had a stroke while supported with the BH, mainly thromboembolic, despite aggressive anti-coagulation regimens. Conversely, 31% of children required re-exploration for mediastinal bleeding. Thromboembolic and hemorrhagic complications were both frequently seen in the same patient. This fits with previous reports reflecting the inherent risks with the BH pump.[9–11] Reducing this is likely to depend on device developments. The stroke risk of $< 10\%$ achievable with the third- and fourth-generation adult centrifugal pumps is currently only an aspiration in pediatrics.[14]

The UK BH program has been an undoubted success in supporting children with heart failure to transplant who would otherwise have died. But, it has highlighted the limited organ availability for such children. The growth of the donation after circulatory death program means the number of hearts offered for donation may well fall. Although cardiac donation after circulatory death has been used, this remains controversial.[15] Successful future management of children listed for heart transplantation depends on improved organ availability together with the development of MCS technology. Without this, increasing referrals can only mean that children will wait longer with ongoing significant attrition.

Approximately 8 children listed for heart transplant die each year in the UK. To support these children is likely to require significant capacity increases between the 2 transplant

centers. In the recent era, more than 50% of pediatric heart transplantations in the UK are urgently listed patients on MCS. It is now rare for a child to receive a transplant when relatively well, which effects his or her postoperative course and hospital length of stay. Effectively, we have moved into an era of higher-risk pediatric cardiac transplantation by rescuing children who would otherwise have died. This is reflected in an increased mortality risk in the immediate post-transplant period compared with children who require medical support only pre-transplant, but 1-year conditional survival is equal and remains high.[16,17]

In conclusion, the UK BH program has allowed significant increases in the number of children offered MCS as a BTT and the length of time that they can be safely supported. Although younger children have significantly longer waiting times during VAD support, their outcomes are comparable to older children. The total number of transplants has remained static, and a significant number of children still die waiting.

Disclosure statement

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