European Journal of Cardio-Thoracic Surgery 51 (2017) 709–714
doi:10.1093/ejcts/ezx006 Advance Access publication 16 February 2017

ORIGINAL ARTICLE

Cite this article as: Nassar MS, Hasan A, Chila T, Schueler S, Pergolizzi C, Reinhardt Z *et al.* Comparison of paracorporeal and continuous flow ventricular assist devices in children: preliminary results. Eur J Cardiothorac Surg 2017;51:709–14.

Comparison of paracorporeal and continuous flow ventricular assist devices in children: preliminary results†

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Received 5 September 2016; received in revised form 6 December 2016; accepted 11 December 2016

Abstract

OBJECTIVES: With the scarcity of organs, a durable, reliable ventricular assist device (VAD) is required. The Berlin Heart EXCOR® (BH) remains the most established VAD in the paediatric population. Implantable continuous flow (CF) VADs have been introduced to the paediatric field with encouraging early results. In this study, we compared the results of a newly introduced CF VAD (HeartWare VAD [HVAD]®) to results in a matched group of BH recipients.

METHODS: The study included patients aged <16 years who received mechanical left VAD (LVAD) support between December 2005 and January 2016. The preimplant characteristics and postimplant outcomes of patients who received the HVAD were compared with those of a matched group who received the BH. Patients with congenital heart disease were excluded.

RESULTS: Thirty patients were included in the study: 13 had received the HVAD and were matched with 17 patients who had received the BH LVAD. The only difference in preimplant characteristics was the need for higher inotropic support in the BH group. There was no difference in the need for right ventricular (RV) support (58.8% for BH vs 53.8% for HVAD, $P = 1.00$) or in the incidence of cerebrovascular accidents (12.5% vs 7.7%, respectively, $P = 1.00$), though the BH group showed prolonged mechanical ventilation (31.3% vs 0%, $P = 0.047$). There were no deaths while on VAD support in either group. Patients with the HVAD showed a bimodal distribution for the primary end point (transplant/explant): All HVAD recipients who also required early RV support reached this end point within 30 days of receiving the implant.

CONCLUSIONS: Our early experience with the CF intracorporeal LVAD system (HVAD) indicates outcomes comparable to those with the well-established pulsatile flow paracorporeal LVAD (BH). The theoretical durability of the CF device, which might also allow for the possibility of hospital discharge and better quality of life, is yet to be proven.

Keywords: Ventricular assist device • Berlin Heart • HeartWare • Paediatric • Mechanical support • Heart failure • Durability • Continuous • Pulsatile

INTRODUCTION

Because of the dismal outcome of heart failure in children, cardiac transplant remains the most valid option for those who are the sickest [1]. When medical treatment fails to stabilize these patients, mechanical circulatory support is a necessity. Although extracorporeal life support is the most accessible treatment option for many cardiac centres, especially in acute situations, it fails to provide reliable, durable support for more than a few weeks [2, 3]. A ventricular assist device (VAD) plays a vital role in bridging patients to transplant. Currently, the Berlin Heart EXCOR® (BH) remains the most established VAD in the paediatric population because it has small pumps that can support different age groups. Its superiority to extracorporeal membrane oxygenation has been established in the first and only multicentre prospective trial of a paediatric VAD [3]. Durability of mechanical circulatory support in children may be defined as long-term, event-free survival while on support with the prospect for hospital discharge and improved quality of life (QOL). As such, there is considerable room for improvement in the durability offered by extracorporeal devices such as the BH.

In adults with end-stage acquired cardiomyopathy, use of intracorporeal continuous flow (CF) assist devices has increased

†Presented at the 30th Annual Meeting of the European Association for Cardio-Thoracic Surgery, Barcelona, Spain, 1-5 October 2016.

substantially with excellent patient mobility and low complication rates. The use of these devices in the paediatric population is constrained mainly by small patient size. Although we and others have reported early experiences with intracorporeal CF (HeartWare® ventricular assist device [HVAD]®) devices in the paediatric population with encouraging early results [4–7], no comparative studies with the BH system have been reported. The objective of this study was to examine the outcomes of implantation of the HVAD in children and to compare these outcomes with those of a matched group with the BH.

MATERIALS AND METHODS

This single-centre retrospective cohort study was performed on a case-matched control series including patients who underwent left VAD (LVAD) implantation at the Freeman Hospital between December 2005 and March 2016. During that period, 128 children had received VAD support; of those, 97 had the BH and 14 patients received the HVAD (the first HVAD case was in 2010; the majority were implanted between 2014 and 2016). We used our department database to select children younger than 16 years of age who were destined to receive an LVAD for left ventricular dysfunction. Those with significant right ventricular (RV) failure who were to receive a simultaneous biventricular assist device and those with congenital heart disease were excluded from the study. Institutional approval of study design was obtained and need for consent was waived considering the retrospective nature of the study.

Our criteria for LVAD implant/explant as well as our strategy to optimize RV function and avoid RV support were reported previously. Our current strategy is to offer an HVAD whenever it is feasible and when no need for an RVAD is anticipated [7, 8]. Thirteen patients with an HVAD met the inclusion criteria (HVAD group) and were matched to 17 patients in our BH population who met the study criteria (BH group). Matching criteria were age, weight and diagnosis. Occasionally, more than 1 patient could be matched for a control, which explains the difference in numbers between the 2 groups. We compared preimplant characteristics and postimplant outcomes of the 2 groups with the aim of identifying any statistically significant differences.

The preimplant characteristics used for comparison included demographic data, diagnosis and clinical severity. Indicators for clinical severity were need for inotropic support (using the vasoactive-inotropic score) [9], length of stay in the intensive care unit, the Interagency Registry for Mechanically Assisted Circulatory Support score [10] and end-organ hepatorenal dysfunction immediately prior to VAD implantation (model for end-stage liver disease [MELD]-XI score) [11].

The vasoactive-inotropic score = dopamine dose (mcg/kg/min) + dobutamine dose (mcg/kg/min) + 100 × epinephrine dose (mcg/kg/min) + 10 × milrinone dose (mcg/kg/min) + 10 000 × vasopressin dose (units/kg/min) + 100 × norepinephrine dose (mcg/kg/min)

$$\text{MELD} - \text{XI score} = 11.76\ (\log_e \text{creatinine}) + 5.112\ (\log_e \text{total bilirubin}) + 9.44$$

The outcomes of both groups were compared with regard to primary end-points (death, recovery or heart transplant) or secondary outcomes, which included need for prolonged, aggressive inotropic support, need for right side support (as a result of non-coping RV following LVAD insertion), prolonged ventilation, surgical reintervention, infection, cerebrovascular accidents (CVA; ischaemic or haemorrhagic), gut ischaemia leading to laparotomy, limb loss, tracheostomy, hepatic or renal impairment (at day 10 postimplant). We further analysed all patients ($n = 30$) as a single cohort to examine for predictors of death or major complications.

Statistical analysis

Continuous data were reported as the mean ± standard deviation (SD) or as the median with the stated range. A comparison of means between groups was performed using the unpaired *t*-test. Comparisons for variables with multiple ordinal or nominal scores were performed using the non-parametric Kruskal–Wallis test; binomial data were expressed as proportions and a comparative univariable analysis was performed using the Fisher's exact test. The Kaplan–Meier analysis was used for survival with the log-rank test used to determine significant differences. A probability value of <0.05 was taken to represent statistical significance. Analyses were performed using the IBM Statistical Package for the Social Sciences version 22 (Statistical Package for the Social Sciences Inc., Chicago, IL).

RESULTS

Preimplant characteristics

A comparison between the 2 groups is shown in Table 1. As expected, there were no significant differences in age and weight between the 2 groups because both criteria were used for matching. The third matching criterion was clinical diagnosis with dilated cardiomyopathy being the most frequent in both groups: 13 children (76.5%) in the BH group and 9 children (75%) in the HVAD (Fig. 1) group. Other clinical diagnoses included 1 restrictive cardiomyopathy, 1 acute graft failure, 1 hypertrophic cardiomyopathy and 1 myocarditis in the BH group. In the HVAD group, 1 child had myocarditis, 1 had restrictive cardiomyopathy, 1 had hypertrophic cardiomyopathy and 1 had acute graft failure (Fig. 1). The patient in the BH group with acute graft failure was briefly bridged with extracorporeal cardiac life support and recovered after 42 days of BH support. The child in the HVAD group was given the HVAD after LV dysfunction secondary to acute rejection and retransplanted after 275 days of support. Both children had episodes of infection while on VAD related to their immunosuppressed state and were managed conservatively.

Though not used as a matching criterion, the preimplant state in both groups was similar in terms of the need for preimplant extracorporeal life support, mechanical ventilation and ICU stay before VAD implantation. Neither group showed any significant difference in the Interagency Registry for Mechanically Assisted Circulatory Support score or end-organ dysfunction (MELD-XI score). Further, there was no significant difference in the proportion of patients with INTERMACS 1 status between groups. However, the inotropic support level (vasoactive inotropic score) was significantly higher in the BH group (Table 1; $P = 0.044$).

Postimplant outcome

Twenty-nine patients reached the primary end point (26 received a heart transplant; 2 in the BH group and 1 in the HVAD group were weaned off support); 1 patient is still on HVAD support

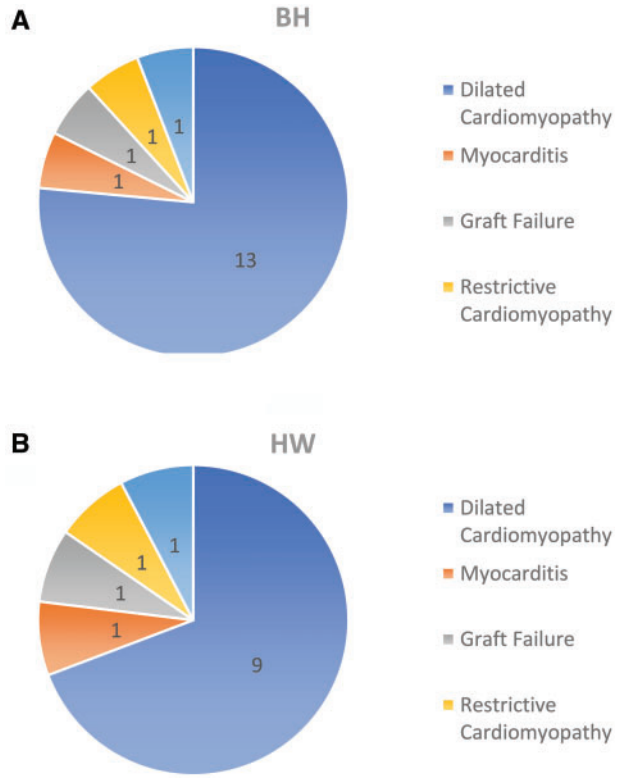

Figure 1: Patient clinical diagnosis based on ventricular assist device type. (**A**) Patients receiving the Berlin Heart (BH). (**B**) Patients receiving the HeartWare ventricular assist device.

(over 600 days of support at present). Median follow-up in the BH group was 6.3 (0.04–10.4) years; median follow-up in the HVAD patients was 1.4 (0.1–6.3) years. Follow-up was complete in all patients until March 2016. There were no deaths in either group while the patients were on the VADs. Two patients (1 in each group) died early following heart transplant: The patient who had been supported with the BH developed a catastrophic cerebral event, whereas the child who had been assisted with the HVAD had irreversible multiorgan failure and fungal sepsis.

The postimplant outcome is shown in Table 2. Biventricular support was offered to approximately half of the children in each group (58.8% in the BH and 53.8% in the HVAD group, respectively), with the biventricular assist device BH and the LVAD HW plus the RVAD Levitronix, respectively. Among the 7 patients from the HW group on biventricular support, 6 required RVAD support at the time of HW insertion and 1 required late RVAD support (BH-RVAD) 73 days after the first procedure. Five patients received a temporary RVAD with the Levitronix. The remaining 2 patients received a long-term RVAD, the BH RVAD. In the BH group, 7 required RVAD insertion at the time of LVAD insertion whereas 3 required subsequent early RVAD insertion (postoperative day, 1–18).

The incidence of major complications was low in both groups with CVA occurring in 12.5% and 7.7% in the BH and HVAD groups, respectively. When correcting for duration of support (mean of 59.2 days for BH vs 128.9 days for HVAD), the incidence of CVA was two-fold higher in patients receiving the BH (0.01 events/patient/100 days of support) compared with those receiving the HVAD (0.005 events/patient/100 days of support). There was no significant difference in event-free survival at 1 year between the 2 groups (Fig. 2). Two patients in the HVAD group suffered device thrombosis. One was successfully decommissioned and the second received successful thrombolysis. In the BH group, 8 patients required a total of 12 ventricle changes. Three patients in the HVAD group were discharged home (1 was

Table 1: Preimplant characteristics

Variable	BH group ($n = 17$)	HVAD group ($n = 13$)	*P*-value
Age at implant, years	6.57 ± 4.1	8.72 ± 4.4	0.18
Weight at implant, kg	20.62 ± 10.6	29.3 ± 15.4	0.08
Gender, male/total (%)	8/17 (47.1)	8/13 (61.5)	0.49
VIS	15.57 ± 10.06	8.62 ± 6.1	0.04*
Serum albumin, g/l	37.9 ± 6.2	40.1 ± 10.5	0.53
MELD-XI score	14.1 ± 5.7	16.6 ± 9.4	0.41
ICU stay, days	7.9 ± 9.6	7.1 ± 9.7	0.81
INTERMACS score[a]	1.0 (1-4)	2 (1-3)	0.44
INTERMACS 1 score (%)	10/17 (58.8)	6/13 (46.2)	0.73
ECLS (%)	5/17 (29.4)	2/13 (15.4)	0.43
Mechanical ventilation, *n*/total (%)	12/17 (70.0)	8/13 (61.5)	0.71
CPR, *n*/total (%)	2/17 (11.8)	2/13 (15.4)	1

When not otherwise specified, the values are expressed as mean ± SD.
[a]Median (range).
BH: Berlin Heart; HVAD: HeartWare ventricular assist device; VIS: vasoactive-inotropic score, serum albumin and MELD-XI values at day 1 before implantation of the ventricular assist device; MELD: model for end-stage liver disease; ICU: intensive care unit; INTERMACS: Interagency Registry for Mechanically Assisted Circulatory Support; ECLS: extracorporeal life support; BSA: body surface area; CPR: cardiopulmonary resuscitation.
*$P < 0.05$.

Table 2: Postimplant outcome

Variable	BH group ($n = 17$)	HVAD group ($n = 13$)	*P*-value
BiVAD, *n*/total (%)	10/17 (58.8)	7/13 (53.8)	1
VIS	6.6 ± 6.4	8.2 ± 5.9	0.49
Inotrope duration, days	13.3 ± 20.8	25.5 ± 20.6	0.12
Mechanical ventilation duration, days	17.9 ± 16.8	6.4 ± 5.7	0.03*
MELD-XI	12.7 ± 5.9	14.8 ± 8.8	0.49
Serum albumin, g/l	34.6 ± 4.8	32.1 ± 4.7	0.19
RRT, *n*/total (%)	3/16 (18.8)	3/13 (23.1)	1
Surgical reintervention, *n*	1 ± 1.2	0.7 ± 0.8	0.43
Infection or sepsis, *n*/total (%)	11/16 (68.8)	6/13 (46.2)	0.27
CVA, *n*/total (%)	2/16 (12.5)	1/13 (7.7)	1
Laparotomy, *n*/total (%)	0/16 (0)	2/13 (15.4)	0.19
Limb loss, *n*/total (%)	1/16 (6.3)	0/13 (0)	1
Tracheostomy, *n*/total (%)	5/16 (31.3)	0/13 (0)	0.05*
Duration of support, days	59.2 ± 43.2	128.9 ± 141.1	0.06
Overall survival, *n*/total (%)	16/17 (94)	12/13 (92)	1

When not otherwise specified, the values are expressed as mean ± standard deviation.
MELD-XI and serum albumin values at day 10 postimplantation of a ventricular assist device.
BH: Berlin Heart; HVAD: HeartWare ventricular assist device; BiVAD: biventricular assist device; VIS: vasoactive-inotropic score; MELD: model for end-stage liver disease; RRT: renal replacement therapy; CVA: cerebrovascular accident.
*$P < 0.05$.

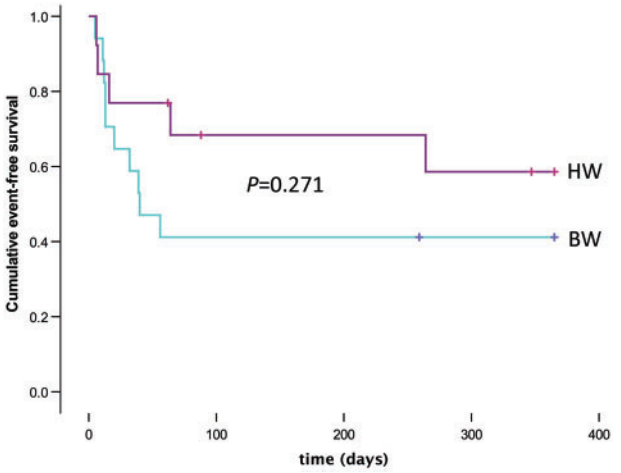

Figure 2: Freedom from death or major complication at 1 year based on the type of ventricular assist device. BH: Berlin Heart; HW: HeartWare ventricular assist device.

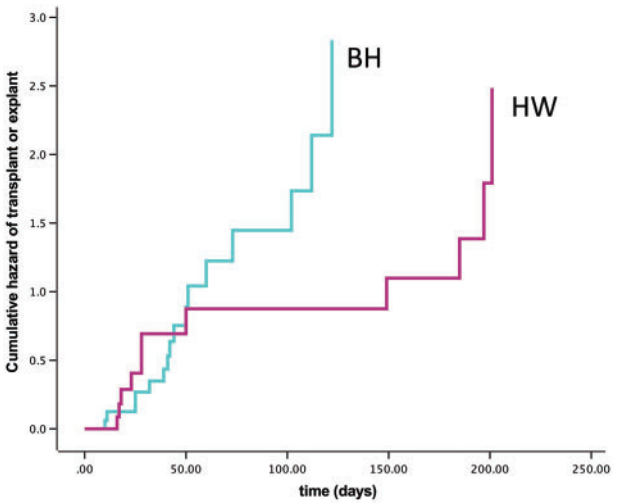

Figure 3: Cumulative hazard function at the moment of primary outcome. BH: Berlin Heart; HW: HeartWare ventricular assist device.

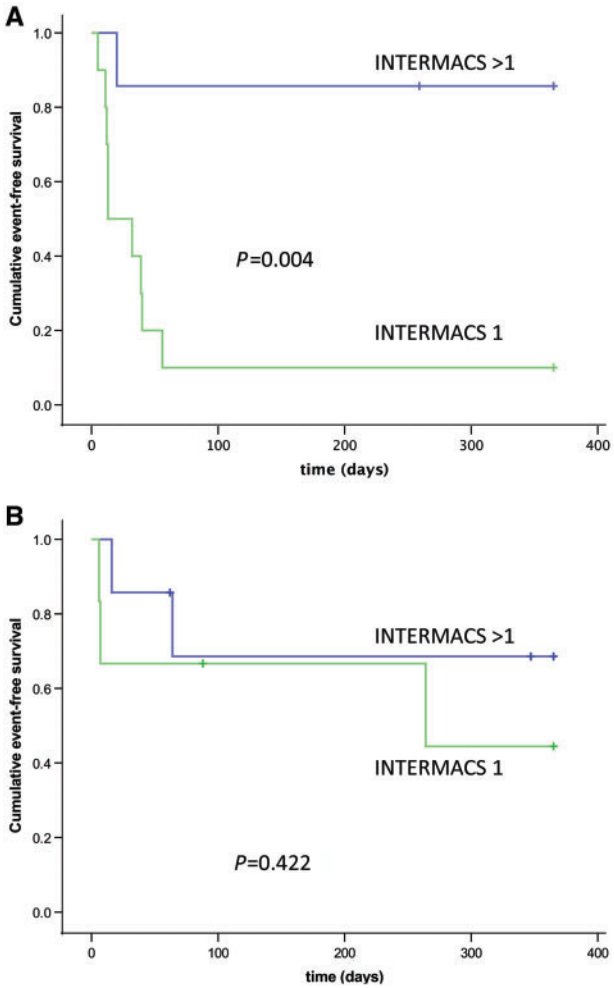

Figure 4: Freedom from death or major complications (cardiovascular accident, laparotomy, limb loss, tracheostomy, sepsis) at 1 year according to Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS)-1 status. (**A**) For patients with paracorporeal pulsatile flow devices: Berlin Heart®; (**B**) for patents with intracorporeal continuous flow devices: HeartWare® ventricular assist device.

weaned after the device thrombosis episode and 2 received transplants later); a fourth patient could not be discharged from hospital due to social issues (now in hospital with over 600 days of support). Two patients were successfully discharged home and able to attend school/nursery.

The cumulative hazard function for the primary outcome of death/transplant or explant revealed a striking bimodal hazard in the HVAD group, in contrast to the steadily increasing hazard seen in the BH group (Fig. 3). Thus, the patients in the HVAD group appeared to be segregated into 2 subgroups: the first comprising those who received a transplant early (within 50 days) and the second group including those who received support for a much longer time. Of note, all patients who required early RVAD support were in the first group and received a transplant within 30 days of HVAD implantation. When we examined all patients as a single cohort ($n = 30$), VAD type did not differentiate those with lower event-free survival ($P = 0.46$). Although there was no difference in the proportions of patients with INTERMACS 1 status between the groups, patients with pulsatile flow devices who had INTERMACS 1 status exhibited significantly poorer event-free survival at 1 year (Fig. 4A; $P = 0.004$), whereas those who had received CF devices did not (Fig. 4B; $P = 0.422$).

DISCUSSION

The VAD has become the standard of care for paediatric end-stage heart failure as a bridge to transplant with an evident reduction in the number of deaths among those on the waiting list [12]. Numbers from the UK paediatric heart transplant service show that more than 50% of children who receive a heart transplant are bridged with a VAD [13]. Disadvantages and complications seen with the BH, an early generation paracorporeal device, have pushed centres to explore the possibility of applying third generation CF devices, which are, thanks to technological advances, now available in relatively small sizes. In the most recent INTERMACS report, the paediatric registry (PediMACS) shows how the CF implantable devices started to predominate in children above 5 years of age, with 56% of patients between 6 and 10 years of age and 90% of older children receiving an implantable device [14]. Most of the outcome data for the CF VAD are

from experiences with adults, and a comparison between both available options for the paediatric population was always biased by differences in patient characteristics [15, 16]. In this study, we tested the theoretical advantage of using the implantable VAD (HVAD) compared with a matched group of those receiving the BH. Our results demonstrate comparable outcomes between the 2 VAD types in terms of incidence of complications and overall event-free survival at 1 year, with only INTERMACS-1 status being associated with a poorer outcome.

The main advantage of implantable CF devices, and hence the HVAD, is their portability, which allows patients to be discharged home and to go back to activities of daily life [17]. Discharge home is possible in the adult population [18] and should, at least theoretically, be the case in the paediatric population supported with an implantable VAD, a point that would improve the QOL for these hospital-bound kids. Though studies have shown that QOL following transplant was not worse in those children who were bridged with a VAD [19], the only study that looked at the QOL while on VAD support has shown that those patients have a lower QOL compared to healthy children or even comparable patients with severe cardiac disease [20]; that study included 13 patients (10 BH and 3 HVAD). Unfortunately, the numbers were too small to compare the QOL between the 2 groups. Their interpretation for this result was that the patients with a VAD have significant limitations in physical activity, which an implantable CF device (HVAD) could overcome. In our experience, hospital discharge was possible for 4 patients (2 attending school/nursery). Although these 4 represented only 30% of those receiving our small HVAD series, additional experience would allow us to improve patient selection, which would in the end prove this theory.

A relatively low incidence of CVA is another purported advantage of CF devices. Our results are similar to those of Carbera *et al.*, who reported the outcome with the HeartMate II in the paediatric population [16]. BH devices are associated with a higher incidence of CVA. In the milestone prospective randomized control trial of the paediatric VAD, there was a 29% incidence of new strokes [3]. Stein *et al.* [15], looking at a contemporary paediatric cohort in a single program, described a stroke risk of 24% for pulsatile-flow devices and 11% for continuous-flow devices. However, recent reports show a lower incidence of CVA with the BH VAD with application of a strict anticoagulation protocol and nursing education. Byrnes *et al.* [21] reported a current incidence of 16%, a result replicated by Miller *et al.* [20] in their small series. Those results are similar to our results. If the reduction in the incidence of CVA with the BH holds for a longer duration of support, this advantage of the HVAD would be less important.

The need for prolonged mechanical ventilation in the paediatric population receiving VAD support is well recognized and reflects the poor general condition of those patients before the implant that continues for a period following VAD insertion. Prodhan *et al.* reviewed the risk factors for prolonged mechanical ventilation after VAD implant. In their series of 43 paediatric patients who received a BH, 33% required prolonged mechanical ventilation until transplant or death [22], a result which is similar to that of our BH group, with 31% of the patients requiring tracheostomy, which we have used as an indicator for prolonged mechanical ventilatory support. On the other hand, in a multicentre report of the use of HVAD in the paediatric population, prolonged ventilation was labelled as one of the morbidities of HVAD implantation in children [4]. Our results show that prolonged ventilation is still a problem; however, it is significantly less frequent than that seen in the patients receiving the BH. This result could in part be due to selection bias towards less morbid patients in the newly introduced HVAD program, though the preimplant clinical conditions were similar between our 2 groups except for the higher preimplant inotropic support in the BH group.

With a growing waiting list, the need for a reliable durable device is urgent. Implantable CF devices have proven durability, with around 40% of implants in adults labelled as destination therapy [14]. In our study, the HVAD group had a longer duration of support that was close to significance ($P = 0.06$), keeping in mind that one of the HVAD has not yet reached the end point, with over 600 days of support. What is interesting is the bimodal hazard for the primary end point of death/transplant/explant observed in the HVAD group where all patients requiring early RVAD received a transplant within 30 days of implantation; this situation has not been previously described. The need for RVAD support after LVAD implantation is recognized in children because paediatric heart failure is often associated with biventricular dysfunction or elevated pulmonary vascular resistance [4, 23]. Our results showed no difference between either modality in terms of the need for RV support. Takeda *et al.* [24] reported a similar result in the adult population, with the difference in the percentage being significantly higher in children. The reported incidence of RV failure requiring VAD support in children is 10–50% [14, 22, 25]. This wide difference between reports reflects the fact that there are no definite criteria for biventricular assist device rather than LVAD support. The need for early RVAD support, even temporary, has limited device durability in a group of our patients. This difference could not be explained by the fact that the experiences occurred early because the need for RVAD was the same for our group receiving the BH. It is simply an indication that more objective criteria are required to define those unlikely to require RV support and subsequently benefit most from implantable devices.

We did not observe a difference in postoperative recovery between the 2 groups except for the longer ventilation support in the BH group. This result was further confirmed because the type of VAD was not a predictor of major events when we analysed all patients as a single cohort. Only preoperative status (presented by INTERMACS score) was an independent predictor of major events.

Limitations

In addition to the retrospective nature of this study, the small sample size limits the ability to make definite conclusions or perform subgroup analyses to identify patients who are likely to require RVAD support and, as such, benefit less from a CF device. Our study is therefore underpowered to detect small differences between groups. Another limitation is that, in order to match patients, the study was carried out over a 10-year period, and changes in evolving clinical protocols may be important, particularly given that implantation of a CF device is a recent innovation. The study does, however, include patients from our early experience with the BH, which could compensate for this effect. The smallest child to receive an HVAD in our cohort weighed 13.5 kg. Implantation of an LVAD in smaller children is currently unlikely due to device size constraints. In this group of patients, paracorporeal devices remain the only available option.

CONCLUSION

This study confirms our previous report of the feasibility of using the HVAD in the paediatric population; we were able to implant the device in children as small as 13.5 kg (0.6 body surface area). In addition, it suggests that the results of implantable CF devices in this group of patients are not inferior to those of paracorporeal pulsatile VADs (BH). We believe that the results of the present study will prove useful for designing future prospective, larger multicentre studies that might clarify further the role of implantable CF versus extracorporeal pulsatile devices in the management of paediatric heart failure.

ACKNOWLEDGEMENTS

We are grateful to Gareth Parry and Neil Wrightson for assistance in the care and management of all patients included in this study.

Conflict of interest: Stephan Schueler discloses a financial relationship with HeartWare.

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