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ORIGINAL ARTICLE

Clinical Experience With Berlin Heart Excor in Pediatric Patients in Argentina: 1373 days of Cardiac Support

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Abstract The objective of this study was to describe our experience (1373 days of support) with the Berlin Heart Excor (BH) ventricular-assist device (VAD) as bridging to cardiac transplantation in pediatric patients with end-stage cardiomyopathy. This study involved a retrospective observational cohort. Records of patients supported with the BH VAD were reviewed. Data regarding age, sex, weight, diagnosis, preoperative condition, single *versus* biventricular support, morbidity, and mortality were collected. Criteria for single versus biventricular support and intensive care unit management were registered. The procedure was approved by our Institutional Ethics Committee, and informed consent was obtained. Between March 2006 and March 2010, 12 patients with diagnosis of dilated ($n = 10$) and restrictive ($n = 2$) cardiomyopathy were supported. Median age was 56.6 months (range 20.1–165.9); mean weight was 18.3 kg (range 8.5–45); and nine patients were female. Every patient presented with severe heart failure refractory to pharmacological therapy. Biventricular support was necessary in four patients. Nine patients underwent heart transplantation. No child was weaned off the BH VAD because of myocardial recovery. Mean length of support was 73 days (range 3–331), and the total number of days of support was 1373. Three patients had fatal complications: 2 had thrombo-hemorrhagic stroke leading to brain death, and one had refractory vasoplegic shock. The BH VAD is a useful and reasonable safe device for cardiac transplantation bridging in children with end-stage heart failure. Team experience resulted in less morbidity and mortality, and time for implantation, surgical procedure, anticoagulation monitoring, and patient care improved.

Keywords Mechanical assist device · Pneumatically pulsatile assist device · Cardiac transplantation · End-stage heart failure · Cardiac failure

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Introduction

Cardiac transplantation still remains the definite treatment available for end-stage dilated cardiomyopathy (DCM) in children. Pediatric patients with end-stage heart failure listed for cardiac transplantation have long wait times, and accessibility to a donor organ is still an important concern [6, 8].

After maximum pharmacological therapy fails, it seems reasonable to implant a long-term mechanical circulatory support (MCS) device. The pediatric-sized Berlin Heart Excor ventricular-assist device (BH VAD; Berlin Heart AG, Berlin, Germany) is a valuable option as a bridge to heart transplantation or recovery for children suffering cardiogenic shock [4].

Many reports of pneumatic paracorporeal VADs mention the advantages of pulsatile device, including long-term support capability, ease of use, biventricular support without oxygenator, patient mobility, and pulsatile flow.

Advantages include the stationary unit IKUS Excor®-Berlin Heart GmbH, Berlin, Germany can operate in various modes (synchronous, asynchronous or separated ventricles) [3]. Different device size may be chosen to fit either neonatal, pediatric, or adult patients. Two triple-leaflet valves made of titanium or polyurethane are located in the output and inlet of the pump to prevent blood reflux. A multilayer flexible membrane separates the blood chamber of the air chamber, and silicon cannulas connect the blood pumps to the patient. Disadvantages include risk of thromboembolic complications, difficulties in cannula implantation and explantation, cumulative costs, infections, and the need to exteriorize the cannula [1].

Current reports have shown that earlier implantation, heparin (Carmeda)-coated internal surfaces, cannula design, and advances in anticoagulation protocols have significantly increased survival and discharge rate, especially in children <1 year old [3, 5, 7, 9, 10].

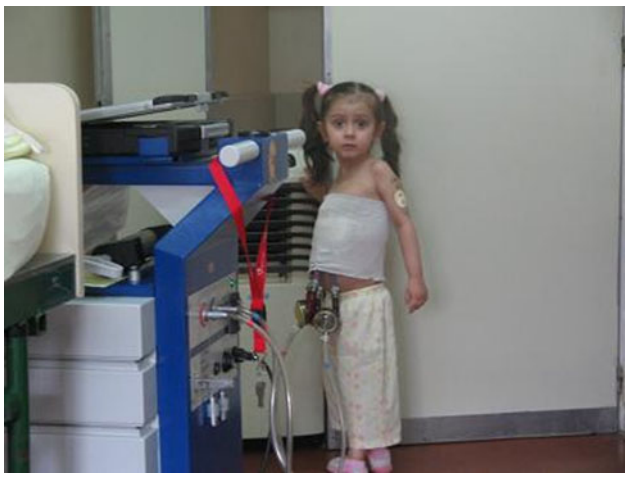
The Hospital de Pediatría "Dr. Juan P. Garrahan" is the most important reference center in Argentina for congenital heart surgery and pediatric cardiac transplantation. Patients from all over the country and from other Latin-American countries are admitted. Waiting time for patients on the emergency transplant list at our institution is approximately 3 months. An MCA program as bridge for transplantation was initiated in 2006 with the BH VAD. The aim of this report is to describe our experience during 1373 cumulative days of support using this device.

Patients and Methods

The clinical records of patients supported with the BH VAD were reviewed. The following data were collected: age, sex, weight, diagnosis, preoperative condition, single versus biventricular support, morbidity, and mortality.

We defined poor preoperative condition as patients with end-stage heart failure leading to progressive damage; hemodynamic deterioration; malnutrition; liver or renal failure with or with out mechanical ventilation (MV); and presence of arrhythmias that may cause sudden death [1, 4, 6]. We consider maximum conventional therapy as epinephrine $\leq 0,2$ mcg/kg/min, phosphodiesterase inhibitors (milrinone $\leq 0,75$ mcg/kg/min), and levosimendan ($\leq 0,3$ mcg/kg/min), respiratory support with MV or noninvasive ventilation (NIV), renal replacement with furosemide and/or peritoneal dialysis, vasodilators, and/or bicarbonate [6].

The BH VAD support procedure was approved by our Institutional Ethics Committee. A multidisciplinary team, including pediatric intensivists, cardiac surgeons, cardiologists, hematologists, and intensive care unit (ICU) nurses, was specially trained for patient care. In every case informed consent was obtained. The criteria for single *versus* biventricular support, ICU considerations, and anticoagulation protocol are described in the Appendix 1. The protocol was reviewed and approved by our Institutional Review Board, and parents' permission to publish the picture was obtained (Picture 1).



Picture 1

Statistical Analysis

Quantitative data presented as medians and SDs or medians and ranks were used as necessary. Categorical and qualitative data are expressed as frequencies of percentages. Data were processed using Stata version 8 software (Stata Corp., College Station, TX).

Results

Twelve patients were implanted between March 2006 and March 2010. Ten patients had DCM, and two had restrictive cardiomyopathy (RCM). Median age was 56.6 months (range 20.1–165.9); median weigh was 18.3 kg (range 8.5–45); and nine patients were female (Table 1).

All patients were on the emergency waiting list for cardiac transplantation and were receiving maximum inotropic support. All patients were mechanically ventilated; four of them underwent tracheal intubation (patients no. 1, 3, 5 and 6; the rest were on NIV). Oliguria was present in every patient despite maximum diuretic use. Two patients had multiorgan failure (patients no. 3 and 5).

Biventricular support was performed in four patients, whereas single left VAD was placed in the other eight

Table 1 Demographic data

Patient no.	Age (mo)	Sex	Weight (kg)	DOS (day)	LOS (day)	VAD type	LP[a]	RP[b]	Diagnosis	Outcome	MV
1	36.03	M	20.00	11	11	B	30	25	DCM	Tx	11
2	56.13	F	14.00	264	339	B	30	25	RCM	Tx	1
3	57.00	F	12.00	146	146	U	30		DCM	D	5
4	126.27	F	31.00	70	70	U	60		DCM	D	8
5	46.00	F	10.00	246	259	U	30		DCM	Tx	10
6	111.37	F	45.00	3	10	B	80	60	DCM	Tx	9
7	53.17	F	15.00	25	25	U	30		DCM	D	16
8	49.77	M	18.00	98	125	B	30	25	RCM	Tx	3
9	85.73	F	18.50	69	76	U	30		DCM	Tx	1
10	122.83	M	23.20	331	345	U	30		DCM	Tx	0
11	165.90	F	23.00	34	43	U	30		DCM	Tx	0
12	20.10	F	8.50	76	123	U	25		DCM	Tx	2

DOS days of support, *LOS* length of stay, *B* biventricular, *U* univentricular, *D* death, *Tx* transplantation, *DCM* dilated cardiomyopathy, *RCM* restrictive cardiomyopathy

[a] Left pump size (ml)

[b] Right pump size (ml)

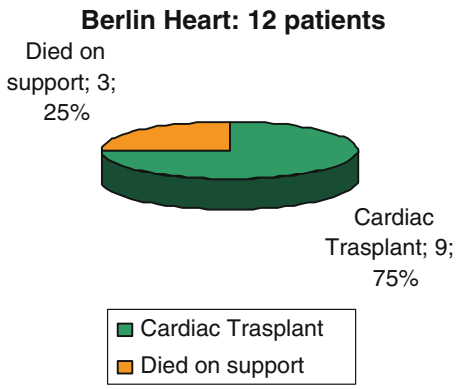


Fig. 1 Proportions of patients achieved cardiac transplantation

Table 2 Complications

Neurological[a]	3	(25%)
Bacteremias[b]	2	(16.6%)
Mediastinitis	1	(8.33%
Pleural effusion (chronic)	1	(8.33%)
Cardiac tamponade	1	(8.33%)

Two strokes and one transitory paresis

[b] *Acinetobacter* sp. and MRSA

patients. In these patients, the right ventricle (RV) was supported with dopamine and milrinone for 3 days until recovery and chronically treated with digoxin, angiotensin-converting enzyme (ACE) inhibitors, and furosemide until cardiac transplantation.

No patient was extubated in the operating room (OR), but the last four patients were weaned off the ventilator on admission to the pediatric ICU (PICU), and two patients were weaned off the day after. Median length of MV support was 5 days (range 0–16). Nine patients (75%) underwent heart transplantation (Fig. 1), and seven of these were discharged home. No child was weaned off the BH VAD without transplantation. Median length of support was 73 days (range 3–331), and the total number of days on the BH VAD was 1373. Three patients had major complications leading to death. The total adverse events are listed in Table 2.

Thromboembolic Episodes

Two patients had severe hemorrhagic stroke leading to brain death. Another patient experienced transitory right-arm paresis without evidence of fibrin or thrombus in the pump surface. The patient's neurological symptoms and 187 days on the BH VAD prompted us to change the pump, in which a large thrombus was found. The patient's outcome was good: She underwent cardiac transplantation and was discharged home. After these events, the anticoagulation protocol was adjusted, and no thromboembolic episodes were detected in any patient in the last 636 days of support. One other pump was changed at day 53 in an otherwise asymptomatic patient who was at risk for clotting, but no thrombus was found. None of the patients presented significant bleeding episodes.

Infections

One patient developed mediastinitis with two retrosternal abscesses. Cultures grew staphylococci and fungi; cephalotin, rifampicin, and fluconazol were started; the abscess

was not drained; and the device was not removed until transplantation without further complications. Bacteriemia without an identified source was detected in two patients. *Acinetobacter* sp. and methicillin-resistant *Staphylococcus aureous* (MRSA) were found in cultures from both patients.

Hemodynamic Complications

Two patients developed pulmonary edema due to fluid overload, which was easily controlled by pump adjustments. The separate rate mode was useful to decrease output of the right pump, thus decreasing pulmonary edema [4]. Two patients with a left VAD (LVAD) presented frequent premature atrial contractions and atrial flutter, which was treated with amiodarone. One patient required synchronized cardioversion to optimize RV function. Another patient underwent cardiac tamponade and required pericardial drainage.

Other Complications

Patient no. 7 died from acute vasoplegic shock on day 25. No evidence of infection or device dysfunction was found. Three patients needed their pumps to be changed: two of them because of thrombus suspicion and another for nonthrombotic membrane dysfunction on day 49. Specially trained personal performed these changes with no complications.

Discussion

The imbalance between donor heart availability and number of pediatric recipients may result in some children dying while on in the emergency wait list for cardiac transplantation [6]. Introduction of an MCS program as a bridge to transplantation may decrease these deaths [2, 8]. In our country, the wait list for a suitable donor can be extremely long, especially for small children. In this scenario, a long-term support, such as the BH VAD, seems a better choice than extracorporeal membrane oxygenation (ECMO).

Poor patient clinical condition improved with long-term support. As cardiac output improved, extubation, inotropic weaning, and nutritional recovery could be achieved. Although it seems reasonable to support patients before multiorgan failure and shock occur, the timing for starting MCS is sometimes a difficult choice [6]. Patients with severe heart failure may decompensate suddenly and should be closely monitored for signs of renal, hepatic, or gastrointestinal dysfunction, poor peripheral perfusion, or neurologic changes. Arrhythmias are also a high risk factor for sudden death [6, 8]. As confidence in this procedure increased, patients were supported in more eligible conditions, and clinical results improved.

Anticoagulation is always a critical issue because the device is placed until cardiac transplantation is performed. We had a difficult time reaching our desired goals for anticoagulation and antiaggregation (see Appendix 1. Whenever these levels were unstable or difficult to achieve, and this usually happens when antibiotic or other drugs are used in an anticoagulation setting, we changed to enoxaparin until a therapeutic range was achieved. None of the patients presented severe bleeding episodes that required stopping anticoagulation or antiaggregation after the first 48 hours of device placement.

Infection is another important matter of concern. Patients supported in a better clinical condition should have less risk of infection because they can be weaned sooner from MV and central lines. Infections around the cannula site of insertion were common in the first patients until a strictly sterile cannula dressing–change protocol was developed by specially trained nurses.

Although no neonates required prolonged hemodynamic MCS in our population, we think this may be possible at some point; however, ethical issues in this group of patients regarding weight, anticoagulation, and neurologic outcome must be addressed.

At present in our institution, patients with postcardiotomy failure are supported for a short time with ECMO or VAD using centrifugal pumps. In the future, some patients needing prolonged MCS (pending cardiac transplantation) may be switched from ECMO to the BH VAD.

The IKUS was easy to manage, and only small setting adjustments were necessary during the intervention. The most important factor guaranteeing optimum membrane movement is cannula insertion, so an imperfect position must be avoided. This will seldom occur if the implant is performed by trained surgeons.

Because these were all high-risk patients, all of them remained in the PICU until heart transplantation. Despite this, many of them were able to participate in different activities in the hospital's playroom, gymnasium, school, and snack bar. Psychological support for these patients and their families was an important issue. Although attractive, we cannot conclude that the same results could be achieved outside the ICU.

Conclusion

The BH VAD was a useful and a reasonable safe tool as bridge to cardiac transplantation in pediatric patients cared by highly trained staff in the PICU. Cumulative experience, together with a better timing for implantation, surgical management, anticoagulation, and patient global care, may

decrease morbidity and mortality for these pediatric patients awaiting heart transplantation.

Appendix 1

Guidelines for ICU Management

Support Indications

Support indications include persistent low cardiac output with rapid worsening of circulation, poor peripheral perfusion, oligoanuria, hepatic failure, acidosis, and central venous saturation < 40%, and echocardiographic cardiac failure despite maximum inotropic support. Clinically relevant ventricular arrhythmias may be associated with increasing inotropic support because of the risk of ventricular fibrillation and death [4, 6, 10].

Implantation is performed in the OR with cardiopulmonary bypass. The inflow cannula is placed in the left-ventricular apex in patients with DCM to obtain better unloading and suctioning of the pump. Atrial cannulation is preferable in the presence of a restrictive LV. The outflow cannula is placed in the ascending aorta. In cases of biventricular VAD (BVAD), a second pair of cannulas is inserted in the right atrium and pulmonary artery [4, 7].

Criteria for Univentricular Versus Biventricular Support

LV support decreases left-ventricular end diastolic pressure, leading to a decrease in RV afterload. This frequently improves RV function, thus avoiding the need for a BVAD. In children with DCM, the choice of univentricular versus biventricular support depends on RV evaluation. If RV function is acceptable, only the LV is supported. In cases of severe RV dysfunction with ascites, hepatic failure, and central venous pressure >20 mm Hg, we prefer biventricular support. In case of moderate RV dysfunction, the choice of type of support is made in the OR. Sometimes the LVAD is implanted; pharmacological RV treatment is optimized (normal doses of catecholamines, milrinone, and afterload decrease with nitric oxide, prostacyclin, oxygen, mild alkalosis); and 1 h later RV function is re-evaluated. If CPV is >15 mm Hg, there is severe dysfunction and tricuspid regurgitation, and lactic acid levels are >3 mmol/l, the RV pump is implanted. In cases of single LVAD support, RV function is evaluated daily with echocardiography during the first week, and patients are treated with digoxin, ACE inhibitors, and diuretics until transplantation [1, 9] (Fig. 2).

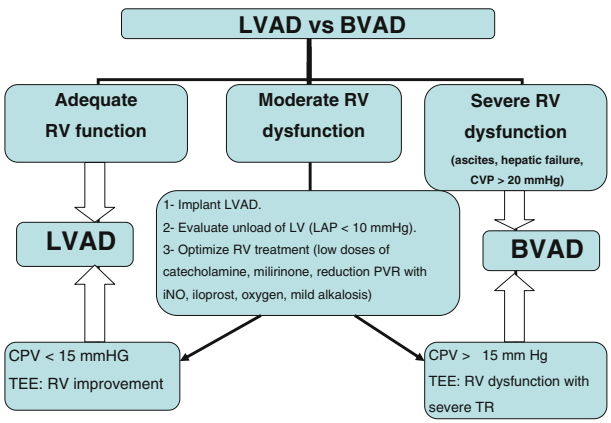


Fig. 2 Algorithm to guide the decision between uni or biventricular support in the operation room

Intensive Care Considerations

Hemodynamic Management

Membrane movement is an important clinical tool with which to evaluate pump stroke volume. There must be harmonic and complete chamber filling and emptying [8]. The afterload increment may deliver inadequate stroke volume (membrane in a convex position). Low pump filling (membrane with wrinkles) is probably secondary to hypovolemia, bleeding, or RV dysfunction (in cases of LVAD). Blood pressure depends on pump settings, volume, and peripheral vascular resistance. Systole length and pump rate are set at the IKUS. Volemia is estimated by direct observation of the membrane. If pump filling is not complete, volume can be administrated; in contrast, if there is incomplete emptying then a diuretic or vasodilator can be used. Vasoconstrictors (norepinephrine, vasopressin) or, most frequently, vasodilators are used to manipulate systemic vascular resistance [9]. Afterload decrease is aggressive to improve pump ejection; continuous sodium nitroprussiate is used early on, and oral ACE inhibitors and/or beta-blockers are administered later.

Nursing Cannula Care

Dressing changes must be performed by specially trained nurses in a strictly sterile environment to prevent mediastinal infections and avoid skin ulceration behind the cannula. When the wound is dry and without infection, dressing changes must be completed once a day for the first 10 to 14 days and then every second day. If the wound is draining and/or appears infected, dressing changes may be performed twice a day. The goal for dressing changes is twice a week if the wound is healing well. Avoid sticking any tape or adhesive on the pumps or cannulas because it is difficult to remove and adversely clouds the transparent material [9].

Visually Monitoring Pumps

Carefully inspect and check the pumps by running a point flashlight over every surface that comes into contact with blood for early detection of clots and fibrin, especially in the valve region. Every 6 h, trained nurses check the pumps and mark a specially designed form. If the beginning of fibrin deposit or clot formation is detected, physicians are informed [9].

Antibiotic Prophylaxis

Empirically, vancomycin is administered to every child within the first 3 days after initiation of support. Meropenem is added if delayed sternum closure is needed.

Enteral Nutrition

Enteral nutrition is started the day after VAD implantation.

Mechanical Ventilation

Synchronized intermittent mandatory ventilation with pressure support is the preferred ventilation mode. Early extubation is performed if the patient's condition allows.

Prophylactic Antithrombotic Therapy

Although there is no standardized antithrombotic regimen, based on the high risk of circuit occlusion and/or embolic complications, anticoagulant and antiplatelet therapy is administered after implantation of the device [4, 9, 10]. Hemostatic laboratory evaluation before VAD placement includes the following assays: complete blood count, prothrombin time (s), INR, activated partial prothrombin time (APTT), thrombin time, fibrinogen, factor V, platelet function test, von Willebrand factor, antithrombin (AT), protein C, protein S, factor V Leiden, and prothrombin 20210 mutation. In the OR, unfractionated heparin (UFH) is administered and reversed completely with protamine sulfate after the end of surgical procedure.

On admission of a patient to the ICU with bleeding, and according to hemostatic laboratory results, cryoprecipitate and/or fresh frozen plasma and/or platelet concentrates are transfused. Antithrombin <70% is corrected with 50 U/kg AT concentrate. During the first 24 h after surgery, no anticoagulation is administered. The contact surfaces of the pump are heparin (Carmeda)-coated, which provides a degree of protection against thrombosis during the first hours until bleeding stops and anticoagulation therapy is initiated.

Twenty-four to 48 h after VAD placement, UFH infusion is initiated if there is no bleeding and/or presence of mediastinal tube drainage <2 ml/kg/day and the platelet count is >20.000/μl. When the platelet count is >100.000/μl, the target APTT is 1.5 to 2.5 times the patient's baseline APTT and corresponds to an anti–factor Xa level of 0.35 to 0.5 U/ ml.

Forty-eight hours after surgery, if the patient is clinically stable, bleeding has stopped, serum certainties levels are normal, and platelets count is >40.000 μl, weaning from UFH to low molecular–weight heparin (LMWH) is performed (anti–factor Xa therapeutic range 0.6–1.0 U/ ml).

In the case of patients >12 months old who are clinically stable, oral anticoagulation with a vitamin K antagonist is initiated. The target INR level is 2.7–3.5. Until the target INR is achieved, simultaneous administration of warfarin and LMWH is maintained. At every moment during support, if the INR level decreases to <2.7, LMWH must be restarted until the desired INR level is achieved.

Postoperative Platelet Inhibition Aggregation Therapy

At 48 h after surgery, if the patient is clinically stable and the platelet count is > 40.000 μl, dypiridamole is administered (4 mg/kg/d split into four doses). Four days after surgery and the removal of all drainage tubes, acetylsalicylic acid (ASA) is administered (1 mg/kg d bid.) Target platelet inhibition with ASA and dypiridamole are achieved when arachidonic acid and adenosine diphosphate (ADP) platelet inhibition is > 70%.

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