Interactive CardioVascular and Thoracic Surgery 2022, 35(3), ivac107
https://doi.org/10.1093/icvts/ivac107 Advance Access publication 9 May 2022

ORIGINAL ARTICLE

Cite this article as: Kremer J, El-Dor A, Sommer W, Tochtermann U, Warnecke G, Karck M *et al.* Long-term paracorporeal pulsatile mechanical circulatory support in adolescent and adult patients. Interact CardioVasc Thorac Surg 2022; doi:10.1093/icvts/ivac107.

Long-term paracorporeal pulsatile mechanical circulatory support in adolescent and adult patients

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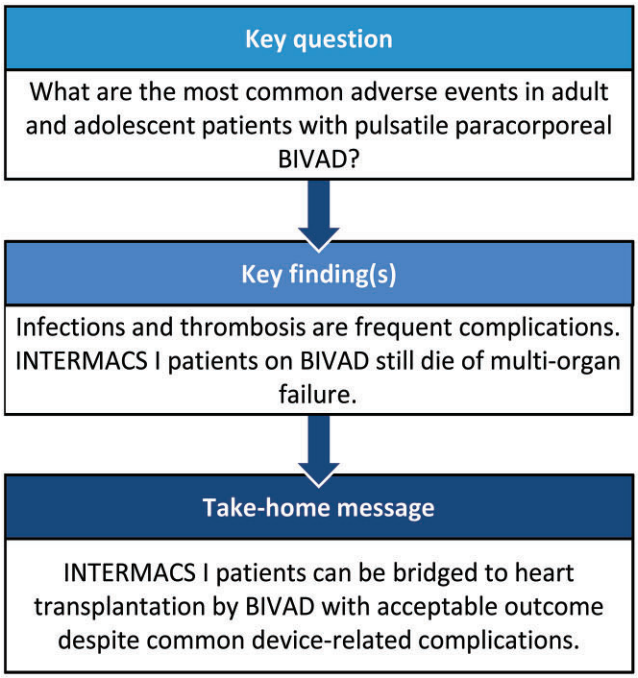
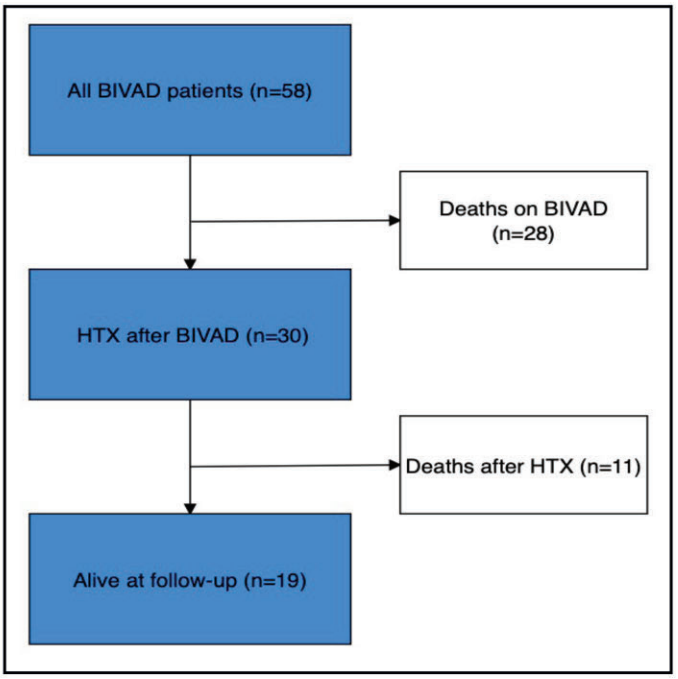
Received 25 January 2022; received in revised form 9 March 2022; accepted 8 April 2022





Abstract

OBJECTIVES: Our goal was to analyse adverse events in adolescent and adult patients with the Berlin Heart EXCOR and to assess the outcome of a subsequent heart transplant (HTX).

METHODS: From 2006 to 2020, a total of 58 patients (12–64 years old) received a biventricular assist device (BIVAD) at our institution and were included in this study.

RESULTS: The causes of biventricular heart failure were nonischaemic cardiomyopathy (62.1%), ischaemic cardiomyopathy (22.4%) and myocarditis (15.5%). The median INTERMACS score was I (I–III). The median age was 49 years (interquartile range, 34–55 years), and 82.8% were male. Causes of death were multiorgan failure (25.0%), septic shock (17.9%), cerebral haemorrhage (14.3%), bleeding (14.3%)

The abstract of this manuscript was presented at the 35th Annual Meeting of the European Association for Cardio-Thoracic Surgery, Barcelona, Spain, 13–16 October 2021.

and embolic events (14.3%). Major bleeding was more frequent in the patients who died while on BIVADs (60.7 vs 6.7%, $P < 0.001$). Wound infections were more prevalent in HTX recipients (n = 21, 70.0%). After BIVAD thrombosis, 104 chamber exchanges were performed in 28 patients (48.3%). HTXs were performed in 52.6% of the patients after a BIVAD support time of 316 ± 240 days. The mean time to follow-up of 30 HTX recipients was 1722 ± 1368 days. One-, 6- and 12-month survival after an HTX were 96.7%, 90.0% and 76.7%, respectively. Long-term survival after 5 and 10 years was 69.7%.

CONCLUSIONS: Pump thrombosis, infections and bleeding after receiving a BIVAD did not preclude a successful HTX. Although only 50% of patients with BIVADs were successfully given a transplant, long-term survival after an HTX in patients with BIVAD was noninferior compared to that of other recipients.

Keywords: Berlin Heart EXCOR system • Mechanical circulatory support • Heart transplantation • Biventricular assist device

INTRODUCTION

Since the first successful implant of a total artificial heart as a bridge to a transplant, performed by Denton Cooley in 1969, ventricular assist devices (VAD) have evolved enormously over the last 2 decades [1]. The introduction of the continuous flow VAD (CF-VAD) as a permanent device has broadened the armory of mechanical circulatory support (MCS). A continuous flow VAD is used predominately as a left ventricular assist device (LVAD) with an off-label option as a right ventricular assist device (RVAD) when implanted either in the right ventricle or more commonly in the right atrium [2]. Currently, the Berlin Heart EXCOR (BIVAD; Berlin Heart, Berlin, Germany) is the only approved device for full biventricular MCS. Another option for biventricular replacement is the SynCardia total artificial heart (CardioWest, SynCardia, Tuscon, AZ). The Berlin Heart EXCOR is a paracorporeal, pulsatile VAD internationally approved for all age groups in patients in need of short-, mid- and long-term biventricular cardiac support. The EXCOR can be used as bridge to recovery or a bridge to a transplant (BTT).

The study by McGiffin *et al.* reports low operative mortality in patients with CF-VADs for biventricular support and encouraging survival after 18 months. However, the risk of RVAD pump thrombosis should not be neglected [3]. A multicentre study reported a 2-year survival of less than 50%, with 34% of their patients being on extracorporeal membrane oxygenation before receiving the biventricular CF-VAD implant. The interval between a left and a right VAD implant had no influence on survival [4].

In the 7th Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) report, 3% of all patients with LVADs needed a secondary RVAD. Only 50% of these biventricular supported patients were alive 1 year after the device was implanted [5].

Because the EXCOR is the only VAD approved for paediatric patients, most device studies analyse paediatric data. The European Registry for Patients with Mechanical Circulatory Support report on primary biventricular support from 2019 included only 5 adult patients with the Berlin Heart EXCOR [6]. Recently, 2 larger studies of adults support by a paracorporeal pulsatile BIVAD showed good survival rates and highlighted the challenges of long-term support [7, 8]. One study focuses on allosensitization in adults before an HTX without further description of adverse events [7]. The second study by Michel *et al.* presents an outcome evaluation of patients in beginning cardiogenic shock who were bridged to an HTX with the Berlin Heart EXCOR [8].

Our study objective was to assess the risks of and the adverse events associated with paracorporeal pulsatile BIVAD support before an HTX. The second purpose of this study was to determine prognostic factors related to survival with a BIVAD while waiting for an HTX and outcome after an HTX.

PATIENTS AND METHODS

Ethics statement

This study complies with the Declaration of Helsinki and was approved by the ethical committee of the University of Heidelberg (S-601/2020). Written informed consent was waived by the issuing committee due to the retrospective nature of the study and the anonymization of the data.

Patient population

All adolescent (>12 years) and adult patients who received a Berlin Heart EXCOR BIVAD from 2006 to 2020 at the University Hospital Heidelberg were included in this retrospective single-centre study. Patient data were collected in a prospective manner until death after a BIVAD was implanted, a successful HTX or death after an HTX. Follow-up was calculated until 31 December 2020. All patients who died were documented, and patients who could not be contacted were lost to follow-up.

Patient demographics, intraoperative data and postoperative outcome data were included in the recorded data.

Surgical implant

The implant technique of the Berlin Heart EXCOR BIVAD at our centre was described previously [9]. Each patient was individually evaluated by a multidisciplinary team of cardiothoracic surgeons, cardiologists and anaesthesiologists. Indication for a BIVAD implant was severe biventricular failure unsuitable for single left ventricular support mostly with primary right ventricular failure. Patients with temporary MCS (62.1%) were evaluated while undergoing stepwise reduction of full cardiac support. The decision to use a long-term BIVAD implant as a BTT was made in cases of unsuccessful weaning of IABP (25.9%), ECLS (50.0%) or both (13.8%) and inotropic support under regular echocardiographic examinations. Organ failure such as hepatic and renal failure was assessed by regular blood chemistry examinations. More detailed cut-off values are presented in the Supplementary Material, Table S1, as described in an earlier publication [10]. The Berlin Heart EXCOR BIVAD implant started with the apex outflow cannula, followed by insertion of the pulmonary artery inflow cannula, the

Table 1: Patient characteristics of the study population depending on when the biventricular assist device was implanted

Characteristics	*All patients (n = 58)*	*Patient died on BIVAD (n = 28)*	*BIVAD to HTX (n = 30)*	*P-value*
***Age,** years*	49 (34–55)	51 (40–59)	45 (33–53)	0.059
***Male** sex*	48 (83%)	21 (75%)	27 (90%)	0.134
***Body mass index**, kg/m²*	27 (22–31)	30 (23–31)	24 (21–29)	***0.017***
Period when the BIVAD was implanted				0.455
2006–2014	34 (59%)	15 (54%)	19 (63%)	
2015–2020	24 (41%)	13 (46%)	11 (37%)	
INTERMACS Profile				0.688
1	40 (69%)	20 (71%)	20 (67%)	
2	11 (19%)	5 (18%)	6 (20%)	
3	7 (12%)	3 (11%)	4 (13%)	
CMP aetiology				0.168
*Non*ischaemic	36 (62%)	13 (46%)	23 (77%)	
Ischaemic	13 (22%)	10 (36%)	3 (10%)	
Myocarditis	9 (16%)	5 (18%)	4 (13%)	
Comorbidities				
Dialysis pre–BIVAD	18 (31%)	12 (43%)	6 (20%)	0.062
Diabetes mellitus	17 (29%)	10 (36%)	7 (23%)	0.276
Hyperlipidaemia	15 (26%)	11 (39%)	4 (13%)	***0.025***
Arterial hypertension	23 (40%)	16 (57%)	7 (23%)	***0.009***
Pulmonary hypertension	31 (54%)	16 (57%)	15 (50%)	0.459
Previous cardiac surgery				
Preoperative support	11 (19%)	8 (29%)	3 (10%)	0.074
IABP	15 (26%)	8 (29%)	7 (23%)	0.652
ECLS	29 (50%)	15 (54%)	14 (47%)	0.602

Continuous data are presented as median (interquartile range) and categoric data as number (%). Bold values indicate statistically significant differences ($P < 0.05$). BIVAD: biventricular assist device; CMP: cardiomyopathy; ECLS: extracorporeal life support; HTX: heart transplant; IABP: intra-aortic balloon pump; INTERMACS: Interagency Registry for Mechanically Assisted Circulatory Support.

Table 2: Intraoperative data from implanted biventricular assist devices

Intraoperative values	*BIVAD implant (Died on BIVAD)*	*BIVAD implant (BIVAD to HTX)*	*P-value*
***Cardiopulmonary bypass time,** min*	232 ± 94	208 ± 38	0.675
***Aortic cross-clamp time,** min*	47 ± 73	25 ± 65	0.231
***Reperfusion time,** min*	19 ± 46	10 ± 21	0.485
***Minimal body temperature,** °C*	34.5 ± 2	35 ± 1	0.196
***Packed red blood cells**, units*	12 ± 8	8 ± 5	***0.011***
***Fresh frozen plasma**, units*	6 ± 7	5 ± 5	0.453
***Operative time,** min*	434 ± 161	400 ± 77	0.396
Urgency of BIVAD			0.960
Elective	3 (11%)	3 (10%)	
Urgent	13 (46%)	15 (50%)	
Emergency	9 (32%)	8 (27%)	
*Ultima ratio/*reanimation	3 (11%)	4 (13%)	
Concomitant cardiac surgery	4 (14%)	0 (0%)	***0.033***
Gortex membrane	16 (57%)	22 (73%)	0.199
***Intensive care unit** in days*	16 (6–40)	19 (5–40)	0.817

Continuous data are presented as mean ± standard deviation or median (IQR) and categoric data as number (%). Bold values indicate statistically significant differences ($P < 0.05$).

right atrium outflow cannular and the anastomosis of the aortic inflow cannula. The pump chambers were connected outside the chest wall after the cannulas were externalized. The cardiopulmonary bypass flow was gradually reduced and the BIVAD pump rate was increased accordingly to achieve a target blood flow of 2.6 l/min/m² body surface area for all patients. Postoperative anticoagulation therapy with heparin was started 24 h after the surgical implant with possible individual modifications. The target international normalized ratio was 3.0–3.5 during follow-up care with an additional 150 mg dipyridamole daily, if ADP activity was lower than 50%, and/or aspirin 100 mg daily if ARA activity was under 30%.

Statistics

All statistical analyses were performed using IBM SPSS Statistics version 25 software (SPSS, Chicago, IL, USA). Normally distributed continuous variables were reported as mean ± the standard deviation and were compared by a two-tailed *t*-test. Categorical

variables were reported as frequencies and percentages and were analysed using the χ^2 test. Survival was calculated using the Kaplan–Meier method. Groups were compared using the log-rank test. The threshold for significance was set at $P < 0.05$. Risk factors for overall mortality were identified using a multivariable logistic regression analysis. Results are presented as the hazard ratio (HR) for long-term mortality with the corresponding 95% confidence interval (CI) and *P*-value.

RESULTS

Patient characteristics

From 2006 to 2020, a total of 58 patients (>12 years) received a Berlin Heart EXCOR BIVAD at our institution. All patients were treated as BTT. The demographic data are shown in Table 1. The aetiologies of biventricular heart failure (HF) needing BIVAD support were nonischaemic cardiomyopathy (62.1%), ischaemic cardiomyopathy (22.4%) and myocarditis (15.5%). A total of 40 patients (69%) were classified as INTERMACS profile I (range: I–III) at the time the BIVAD was implanted. Patients who died while on BIVAD support had a significantly higher BMI (29.5 kg/m^2 vs 24.2 kg/m^2, *P = 0.017*) and a higher frequency of documented arterial hypertension (57.1% vs 23.3%, *P = 0.009*) and hyperlipidaemia (39.3% vs 13.3%, *P = 0.025*). Preoperative MCS support was similar in both groups. The median age was 49 years (IQR = 34–55 years), and 82.8% were male.

The intraoperative data from patients who received BIVAD implants are listed in Table 2. Cardiac procedures concomitant with the BIVAD implants were performed in 4 patients: mitral valve replacement due to structural defects in 2 patients, aortic valve replacement in 1 patient and patent foramen ovale closure in another patient. All 4 patients died on BIVAD support.

Perioperative outcome after a BIVAD

The mean time of BIVAD support was 195 ± 224 days with a total of 11,322 days. The BIVAD support time of patients who died while on BIVAD support was 66 ± 106 days, whereas patients who survived until an HTX had a mean BIVAD support time of 316 ± 240 days; *P < 0.001*. The longest BIVAD support time was 926 days. The Kaplan–Meier survival curve after the BIVAD was implanted is depicted in Fig. 1. One-, 6- and 12-month survival after the BIVAD implant was 74.1%, 43.5% and 38.7%, respectively. The causes of death for the 28 patients (48.3%) who died while on BIVAD support were multiorgan failure (25.0%), septic shock (17.9%), cerebral haemorrhage (14.3%), bleeding (14.3%) and embolic events (14.3%). In total, 35 patients were listed as high urgency) before the HTX.

Adverse events

Postoperative complications after the BIVAD was implanted are listed in Table 3. Overall, 104 chamber exchanges were performed in 28 patients (48.3%) after BIVAD pump thrombosis. Chamber exchanges were performed significantly more often in patients who survived until the HTX (23 vs 5, *P < 0.001*). Out of 28 patients in need of a chamber exchange, 17 patients (60.7%) underwent >1 chamber exchange (range 1–14).

The rate of cerebral haemorrhage was 18% vs 0% *(P = 0.016)* in the group who died while on BIVAD support. In 7 patients (12.1%), cerebral haemorrhagic complications were the direct cause of death. There was also a higher rate of rethoracotomy due to bleeding (39.3% vs 6.7%, *P = 0.003*).

Postoperative dialysis became necessary in 18 patients (31.0%). Patients who died while on BIVAD support presented a significantly higher rate of postoperative kidney failure with a need for dialysis (57.1% vs 6.7%, *P < 0.001*). Of these, 12 patients needed renal replacement therapy before the BIVAD was implanted.

Wound infections were present in 31 patients (53.4%) during BIVAD support. According to the consensus statement of the International Society of Heart and Lung Transplantation, these infections were classified as VAD-specific infections. Additionally, 11 VAD-related infections were documented: 10 primary or catheter-related blood stream infections and 1 mediastinitis. Non-VAD-related infections included 21 urinary tract infections, 7 infections with *Clostridium difficile* and 8 lower respiratory tract infections. Ten patients (35.7%) who died on BIVAD support developed at least 1 wound infection, and 5 patients (50%) developed a wound infection early on (< 30 days after the BIVAD was implanted). The mean time to wound infection was 84 ± 128 days. Wound infections were more prevalent in the group who survived to the HTX (*n* = 21, 70%). The mean time to wound infection in the latter group was 127 ± 172 days.

In the multivariable analysis, arterial hypertension (HR 1.684; 95% CI 1.082–2.620) and postoperative dialysis (HR 7.451; 95% CI 2.749–20.192) were independent risk factors for overall mortality after BIVAD implantation.

Clinical outcome after a heart transplant

The mean time to follow-up of the surviving 30 patients who had HTXs was 1722 ± 1368 days.

One-, 6- and 12-month survival after the HTX was 96.7%, 90.0% and 76.7%, respectively. Long-term survival after 3, 5 and 10 years was 69.7%. Post-HTX causes of death were cardiogenic (*n* = 3), septic shock (*n* = 4), a haemorrhagic stroke (*n* = 1) and 3 causes of death were undetermined due to loss to follow-up. The Kaplan–Meier survival curve after a successful HTX after BIVAD support is presented in Fig. 2.

Ten patients (33.3%) developed at least 1 wound infection after an HTX with 1 death of septic shock attributable to the wound infection. Cerebral stroke was diagnosed in 2 patients (6.7%) after

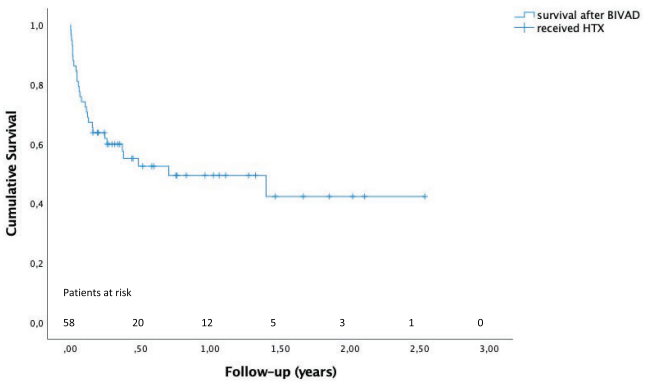


Figure 1: Kaplan–Meier survival curve in years of all patients (*n* = 58) with biventricular assist devices.

Table 3: Complications after a biventricular assist device implant

Characteristics	*All Patients (n = 58)*	*Died on BIVAD (n = 28)*	*BIVAD to HTX (n = 30)*	*P-value*
Pump exchange	28 (48%)	5 (18%)	23 (77%)	***<0.001***
Pulmonary embolism	4 (7%)	2 (7%)	2 (7%)	0.943
Stroke	17 (29%)	8 (29%)	9 (30%)	0.906
Haemorrhagic	5 (9%)	5 (18%)	0 (0%)	***0.016***
Ischaemic	12 (21%)	3 (11%)	9 (30%)	0.072
Major (mRS >3)	9 (16%)	8 (29%)	1 (3%)	***0.009***
Minor (mRS <=3)	8 (14%)	0 (0%)	8 (27%)	***0.004***
Wound infections	31 (53%)	10 (36%)	21 (70%)	***0.010***
Other infections	23 (40%)	13 (46%)	10 (33%)	0.313
Major bleeding	19 (33%)	17 (61%)	2 (7%)	***<0.001***
Rethoracotomy for bleeding	12 (21%)	11 (39%)	2 (7%)	***0.003***
Minor bleeding	7 (12%)	5 (18%)	2 (7%)	0.195
Membrane tear	8 (14%)	2 (7%)	6 (20%)	0.160
Pump thrombosis	25 (43%)	5 (18%)	20 (67%)	***<0.001***
Dialysis post-BIVAD	18 (31%)	16 (57%)	2 (7%)	***<0.001***

Categoric data are presented as number (%). mRS= modified Rankin Score.
Bold values indicate statistically significant differences ($P < 0.05$).
BIVAD: biventricular assist device; HTX: heart transplant.

an HTX. The modified Rankin scale in the first patient was 2; however, the patient died after sternal wound infection and subsequent septic shock. The second patient had a modified Rankin scale of 4 before the HTX. The patient developed intracranial bleeding after HTX and died 167 days later. There were no major bleeding complications after an HTX in this cohort. No readmission for rejection has occurred during the follow-up period.

The multivariable analysis showed that dialysis after an initial BIVAD implant (HR 11.671; 95% CI 1.546–88.120) was an independent risk factor for overall mortality after HTX. However, this patient group only includes 2 patients with post-BIVAD dialysis, both of whom died. Therefore, statistical interpretation should be conducted carefully, and further analysis with a higher number of cases is still needed.

DISCUSSION

Surgical treatment of HF has gained importance in recent years due to the development and improvement of MCS devices. Biventricular support is needed in patients with advanced HF who are ineligible for left ventricular support alone. The Berlin Heart EXCOR offers biventricular support as a bridge to a transplant or to recovery, especially in countries with long HTX waiting list times or fewer financial resources. The costs of a fully incorporeal VAD are listed as being up to 120,000 Euros compared to 20,000 Euros per ventricle chamber of the Berlin Heart EXCOR [11].

The results with biventricular Berlin Heart EXCOR support presented here shed light on the feasibility of this surgical approach and the noninferior survival rate post-HTX in patients with a BIVAD compared to HTX patients with an HTX without previous VAD therapy [7, 8]. Between 2006 and 2020, we implanted 250 permanent MCS devices in patients seen at our centre (BIVAD = 58, HeartWare ventricular assist device = 83, HeartMate II = 5, HeartMate 3 = 104). A biventricular device implant was far less common than a single LVAD implant; however, these 58 patients were too sick for single-ventricle support and would not have had a chance of survival without the option of BIVAD support in the early years. In the recent era, in our centre, bridging of patients in acute HF in hope of recovery, at least of the RV, is predominately done via the ProtekDuo dual lumen cannula (LivaNova, London, UK) for temporary RV support [10]. The goal is for temporary RV support to be sufficient for end-organ function to recover. When patients continued to show clinical signs of prolonged RV failure, they received an EXCOR RVAD. The goal of this analysis was to point out common adverse events and deduce risk factors for mortality and morbidity in this specific patient cohort with paracorporeal pulsatile MCS.

Pal *et al.* state in their review of studies on HTX after VAD that optimal timing needs to be determined, because performing an HTX too early or too late will adversely affect patient survival [12]. The overall support time in our cohort was 11,322 days, with a mean time to an HTX of 316 ± 240 days. These extraordinarily long support times also account for the relatively high rate of adverse events in our cohort. Pump thrombosis, wound infections and bleeding are the main complications while the patient is on VAD support [13]. The most recent studies on BIVAD in adults included 80 patients on the Berlin Heart EXCOR [7, 8]. Wound infections in patients who have the Berlin Heart EXCOR are discussed mainly in paediatric subpopulations. The study by Munoz *et al.* was the first to focus on adult wound infections after a BIVAD implant. They included 15 adult patients and found 5 VAD-specific infections, with all their HTX patients developing at least 1 infection afterwards [11]. We could not identify wound infections to be an independent risk factor for mortality after an HTX nor did they preclude an HTX. The results highlight the importance of prolonged antibiotic therapy in patients with VAD-specific infections before an HTX. Antibiotic treatment was given to treat elevated white blood cell counts, C-reactive protein levels or temperatures as well as after proof of pathological infectious agents at the cannulas. Munoz *et al.* reported an overall post-HTX mortality of 40% in their cohort with no death attributable to a wound infection [11]. Pump exchanges were necessary for pump thrombosis in 48.3% of our patients, in whom we noticed an increasing rate with longer BIVAD support times. However, we could not identify any risk factors explaining the high rate of

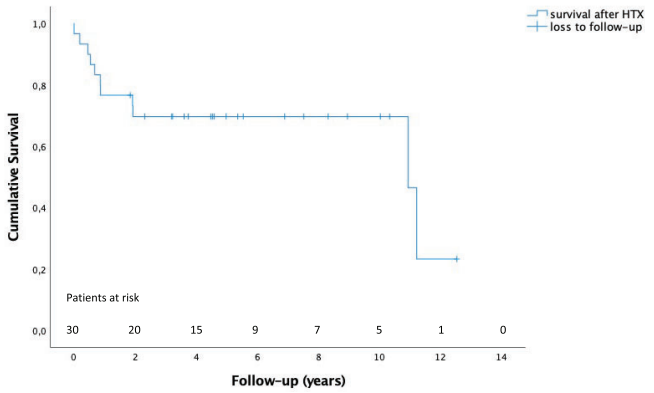


Figure 2: Kaplan–Meier survival curve in years after a heart transplant ($n = 30$).

pump thrombosis. None of the patients with pump thrombosis died, and the patients all underwent successful pump chamber exchanges. Bartfay *et al.* reported that 14% of their group needed intervention for pump thrombosis; about 40% needed pump replacements due to thrombotic deposits in the study by Michel *et al.* [8, 19]. In the latter study, the first pump replacement was indicated after 35.5 days, with a median support time of only 37 days [8].

In a first case series from Krabatsch *et al.* with 2 CF-VADs in biventricular support, the 1- and 6-month survival was 82% and 52%, respectively [14]. Shehab *et al.* reported their results of 13 CF-VADs in biventricular support with an overall mortality of 46% [15]. These numbers are comparable to our results, with a 1-month survival of 75% and a 6-month survival of 44% of all patients with a BIVAD. When comparing a biventricular assist device with the SynCardia total artificial heart, a study by Cheng *et al.* found no significant difference in 30-day and 1-year survival [16]. In a retrospective analysis, Taghavi *et al.* compared post-HTX survival of previous RVAD+LVAD, CF-LVAD and no-VAD recipients and found that the requirement of a permanent RVAD+LVAD before receiving an HTX was independently associated with post-transplant death, whereas immediate perioperative survival was not influenced by the type of MCS pre-HTX. Their hypothesis is that patients with biventricular support are in a better clinical state at the time of the HTX [17]. Nevertheless, recent data from McGiffin *et al.* show superior postimplant outcomes with two HeartMate 3 (Abbott Laboratories, Chicago, IL, USA) CF-VADs [3]. The authors present an actuarial survival rate of 90% after 18 months; in comparison, Kaplan–Meier survival at 1 year and 2 years was 56% and 47%, respectively, in the multicentre study of biventricular MCS with the HeartWare (Medtronic Inc.) CF-VADs by Marasco *et al.* [4]. The favourable outcomes with the HeartMate 3 CF-BIVAD present a valuable new alternative to our presented approach with the paracorporeal pulsatile BIVAD, but larger cohorts are needed to confirm these promising results [3].

Our 1-, 6- and 12-month survival data after an HTX (96.7%, 90.0% and 76.7%) are comparable to other post-HTX survival rates after BIVAD support [7, 8]. The data from the annual report of the scientific registry of recipients, published in 2020, lists an overall 1-year survival of 90.3% for adults who underwent an HTX. The 3-year survival was 84.7%, and 5-year survival was 79.6%, including all listed HTX recipients [18]. Our long-term survival data are comparable to those data, with a survival rate after 3 and 5 years of 69.7%.

Patients with a LVAD with secondary RVAD support who are treated surgically for RV failure have a lower survival rate than those with planned biventricular assist device implants. The goal is for temporary RV support to be sufficient for end-organ function to recover. However, patients who are INTERMACS I often do not profit from temporary support, and about 50% of patients developing secondary RV failure need a long-term device [19]. In a multicentre study from Arabia *et al.* in which 19 centres implanted 38 CF-BiVADs, the adverse events were comparable to our results (Table 3) [20]. With the rising awareness of the need of independent RVAD systems, other than a CF-VAD in the right atrium, the first centres are starting to combine both pumps. In a hybrid approach, 1 Berlin Heart EXCOR pump is implanted for RV support and a CF-VAD as an LVAD. The early results have not yet been published, but clinical data are currently being gathered in different German cardiac surgery centres, including the University Hospital Heidelberg. Although all patients in our study were treated in a biventricular configuration, we offer insight into adverse events and risks embedded in this field of MCS.

With 6 different pump sizes, the Berlin Heart EXCOR offers the possibility to change the chamber size and the pump rate according to the haemodynamic need of the patient. Especially in smaller patients, CF-VADs are often too bulky to fit into the chest. As a paracorporeal device, the Berlin Heart EXCOR is suitable for smaller patients. However, the large wound size under the rib cage should be taken into consideration. Bleeding was a significant complication in our cohort, with a higher rate of major bleeding and a need for a rethoracotomy for bleeding in the patients who died while on the BIVAD, without being an independent risk factor for mortality after the BIVAD is implanted. Significant RV failure can lead to a higher rate of coagulopathy with an increased risk of bleeding during the operation [21]. Even though it showed no statistical significance, patients who had previous cardiac procedures had more major bleeding incidents than patients without previous cardiac procedures ($P = 0.323$). Considering the comparable results from Bartfay *et al.*, implanting an EXCOR BIVAD involves a larger wound area and more potential from bleeding complications when the patient is under anticoagulation [22]. The group from Munich reports bleeding in 42.3% of patients who required re-exploration of the chest [8]. A preoperative extracorporeal life support device or an extracorporeal membrane oxygenation device was not a risk factor for postoperative bleeding. McGiffin *et al.* reported a bleeding rate of 92% in the CF-BIVAD group, without mentioning the rethoracotomy rate for bleeding in their patient cohort with the CF-BiVAD [3].

The results with the Berlin Heart EXCOR presented in this study offer comprehensive insight into this MCS alternative in adult patients. More data are needed for HF physicians to further support this therapeutic option with all its pitfalls and benefits. Multiorgan failure was still the most frequent cause of death in our patients who died while on support but no significant predictors for post-BIVAD multiorgan failure could be identified. However, it is necessary to mention that the small number of cases complicated the statistical significance of this analysis. Most of our patients were INTERMACS I (∼70%); therefore, a poor overall clinical state and poor end-organ function might generally be the reasons for the high rate of multiorgan failure in patients with prolonged biventricular HF. It has been demonstrated that the outcome after long-term MCS in patients in critical cardiogenic shock (INTERMACS profile I) is worse than that in patients with higher INTERMACS profiles [13]. Independent of

ECMO before LVAD implantation, patients classified as INTERMACS I had similar 1-year survival rates of 54 vs 61% in a recently published study by Lamba *et al.* The authors concluded that for critically ill patients for whom palliative care may be the only other option, temporary MCS support before a long-term CF-VAD implant is a valid treatment strategy with an acceptable outcome [23].

Limitations

The limitations of this study include the small number of patients in this cohort. In addition, comparing patients who died on support and patients who survived until an HTX is descriptive in character. Furthermore, experience with the Berlin Heart EXCOR in adult patients is limited. Therefore our study presents relevant information about complications and postoperative challenges with the device for future applications, also in a setting with just an RVAD. A second limitation is the retrospective and observational nature of the study, which limited our statistical analyses.

CONCLUSION

Bridging patients in acute heart failure with temporary devices before long-term MCS in hope of recovery, at least of the RV, is a common strategy with promising results. In patients classified as INTERMACS I, our study demonstrates that at least half of these very ill patients can be successfully bridged to a heart transplant using the Berlin Heart EXCOR. Pump thrombosis, infections and bleeding are the main complications associated with BIVAD support. However, none of these complications precluded a successful HTX after BTT support. Although only 50% of patients with BIVADs had successful transplants, long-term post-HTX survival in patients with BIVADs was not inferior compared to that in other recipients of HTXs.

Data Availability Statement

All relevant data are within the manuscript and its Supporting Information files.

Funding

No funding was received for this work.

Conflict of interest: none declared.

REFERENCES

[1] Slaughter MS, Rogers JG, Milano CA, Russell SD, Conte JV, Feldman D *et al.* Advanced heart failure treated with continuous-flow left ventricular assist device. N Engl J Med 2009;361:2241–51.

[2] Tran HA, Pollema TL, Silva Enciso J, Greenberg BH, Barnard DD, Adler ED *et al.* Durable biventricular support using right atrial placement of the heartware hvad. Asaio J 2018;64:323–7.

[3] McGiffin D, Kure C, McLean J, Marasco S, Bergin P, Hare JL *et al.* The results of a single-center experience with heartmate 3 in a biventricular configuration. J Heart Lung Transplant 2021;40:193–200.

[4] Marasco S, Simon AR, Tsui S, Schramm R, Eifert S, Hagl CM *et al.* International experience using a durable, centrifugal-flow ventricular assist device for biventricular support. J Heart Lung Transplant 2020;39:1372–9.

[5] Kirklin JK, Naftel DC, Pagani FD, Kormos RL, Stevenson LW, Blume ED *et al.* Seventh intermacs annual report: 15,000 patients and counting. J Heart Lung Transplant 2015;34:1495–504.

[6] Vierecke J, Gahl B, de By T, Antretter H, Beyersdorf F, Caliskan K *et al.* Results of primary biventricular support: an analysis of data from the euromacs registry. Eur J Cardiothorac Surg 2019;56:1037–45.

[7] Chaidaroglou A, Armenis I, Gkouziouta A, Bonios MJ, Kogerakis N, Fragoulis S *et al.* The effect of paracorporeal pulsatile biventricular assist devices on allosensitization in adults: a comparison with left ventricular assist devices. Transpl Immunol 2021;69:101477.

[8] Michel S, Buchholz S, Buech J, Veit T, Fabry T, Abicht J *et al.* Bridging patients in cardiogenic shock with a paracorporeal pulsatile biventricular assist device to heart transplantation-a single-centre experience. Eur J Cardiothorac Surg 2022;61(4):942–949. https://doi.org/10.1093/ejcts/ezab547.

[9] Schmack B, Weymann A, Ruschitzka F, Autschbach R, Raake PW, Jurrmann N *et al.* Successful support of biventricular heart failure patients by new excor((r)) adult pumps with bileaflet valves: a prospective study. Clin Res Cardiol 2018;107:413–20.

[10] Kremer J, Farag M, Brcic A, Zubarevich A, Schamroth J, Kreusser MM *et al.* Temporary right ventricular circulatory support following right ventricular infarction: results of a groin-free approach. ESC Heart Fail 2020;7:2853–61.

[11] Munoz P, Valerio M, Vasquez V, Velasquez-Rodriguez J, Sousa I, Zatarain E, "Grupo de Apoyo al Manejo de las Asistencias Ventriculares" (GAMAV) *et al.* Infections in patients after berlin heart((r)) excor assist device implantation. Transpl Infect Dis 2018;20:e12936.

[12] Pal N, Gay SH, Boland CG, Lim AC. Heart transplantation after ventricular assist device therapy: benefits, risks, and outcomes. Semin Cardiothorac Vasc Anesth 2020;24:9–23.

[13] Kirklin JK, Pagani FD, Kormos RL, Stevenson LW, Blume ED, Myers SL *et al.* Eighth annual intermacs report: special focus on framing the impact of adverse events. J Heart Lung Transplant 2017;36:1080–6.

[14] Krabatsch T, Potapov E, Stepanenko A, Schweiger M, Kukucka M, Huebler M *et al.* Biventricular circulatory support with two miniaturized implantable assist devices. Circulation 2011;124:S179–86.

[15] Shehab S, Macdonald PS, Keogh AM, Kotlyar E, Jabbour A, Robson D *et al.* Long-term biventricular heartware ventricular assist device support–case series of right atrial and right ventricular implantation outcomes. J Heart Lung Transplant 2016;35:466–73.

[16] Cheng A, Trivedi JR, Van Berkel VH, Massey HT, Slaughter MS. Comparison of total artificial heart and biventricular assist device support as bridge-to-transplantation. J Card Surg 2016;31:648–53.

[17] Taghavi S, Jayarajan SN, Komaroff E, Mangi AA. Right ventricular assist device results in worse post-transplant survival. J Heart Lung Transplant 2016;35:236–41.

[18] Colvin M, Smith JM, Hadley N, Skeans MA, Uccellini K, Goff R *et al.* Optn/srtr 2018 annual data report: heart. Am J Transplant 2020;20 Suppl s1:340–426.

[19] Takeda K, Takayama H, Colombo PC, Jorde UP, Yuzefpolskaya M, Fukuhara S *et al.* Late right heart failure during support with continuous-flow left ventricular assist devices adversely affects post-transplant outcome. J Heart Lung Transplant 2015;34:667–74.

[20] Arabia FA, Milano CA, Mahr C, McGee EC, Jr., Mokadam NA, Rame JE *et al.* Biventricular support with intracorporeal, continuous flow, centrifugal ventricular assist devices. Ann Thorac Surg 2018;105:548–55.

[21] Konstam MA, Kiernan MS, Bernstein D, Bozkurt B, Jacob M, Kapur NK, American Heart Association Council on Clinical Cardiology; Council on Cardiovascular Disease in the Young; and Council on Cardiovascular Surgery and Anesthesia *et al.* Evaluation and management of right-sided heart failure: a scientific statement from the american heart association. Circulation 2018;137:e578–e622.

[22] Bartfay SE, Dellgren G, Hallhagen S, Wahlander H, Dahlberg P, Redfors B *et al.* Durable circulatory support with a paracorporeal device as an option for pediatric and adult heart failure patients. J Thorac Cardiovasc Surg 2021;161:1453–64 e4.

[23] Lamba HK, Kim M, Santiago A, Hudson S, Civitello AB, Nair AP *et al.* Extracorporeal membrane oxygenation as a bridge to durable left ventricular assist device implantation in intermacs-1 patients. J Artif Organs 2022;25:16–23.