Clinical Research

Outcome of Extracorporeal Ventricular Assist Device for Cardiogenic Shock as a Bridge to Transplantation

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Background: The extracorporeal ventricular assist device (e-VAD) system is designed for left ventricular support using a permanent life support console. This study aimed to determine the impact of temporary e-VAD implantation bridging on posttransplant outcomes.
Methods: We reviewed the clinical records of 6 patients with the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) profile 1, awaiting heart transplantation, who were provided with temporary e-VAD from 2018 to 2019. The circuit comprised a single centrifugal pump without an oxygenator. The e-VAD inflow cannula was inserted into the apex of the left ventricle, and the outflow cannula was positioned in the ascending aorta. The median follow-up duration was 8.4±6.9 months.
Results: After e-VAD implantation, lactate dehydrogenase levels significantly decreased, and Sequential Organ Failure Assessment scores significantly improved. Bedside rehabilitation was possible in 5 patients. After a mean e-VAD support duration of 14.5±17.3 days, all patients were successfully bridged to transplantation. After transplantation, 5 patients survived for at least 6 months.
Conclusion: e-VAD may reverse end-organ dysfunction and improve outcomes in INTERMACS I heart transplant patients.

Keywords: Heart-assist devices, Heart transplantation, Heart failure

Introduction

The shortage of suitable donors and long waiting periods have resulted in a progressive increase in the number of candidates who are bridged to heart transplantation with mechanical circulatory support [1,2]. The procurement and distribution of donated organs in the Republic of Korea are coordinated by the Korean Network for Organ Sharing, a public healthcare network that integrates all hospitals with the capability for organ extraction or implantation in the country. In November 2018, the Health Insurance Review and Assessment Service approved public insurance coverage for durable left ventricular assist devices (LVADs; BerlinHeart Excor, HeartWare LVAD [HVAD]) only in patients who have been approved for a certain period of time.

Peripheral extracorporeal membrane oxygenation (p-EC-MO) plays a major role in determining the treatment strategy for patients with cardiogenic shock. It provides cardio-respiratory support that can be used only as a short-term treatment. However, selected patients who fail to be weaned from p-ECMO may be considered for long-term LVADs.

Nonetheless, durable LVAD implantation is discouraged in patients with cardiogenic shock who are initially safely treated using temporary devices. In the Republic of Korea, temporary extracorporeal continuous-flow LVADs (e.g., Levitronix CentriMag, Maquet Rotaflow, Sorin Revolution) are not imported. Due to accessibility limitations, many heart failure teams consider transition from the p-ECMO system to a durable LVAD as a bridge to heart transplantation.

From a health insurance payer perspective, direct bridging to heart transplantation with a ventricular assist device appears to be more cost-effective than "double bridges" in patients with refractory heart failure [3]. Thus, the extracorporeal ventricular assist device (e-VAD) system is designed for left ventricular (LV) support with a simple circuit configuration using the permanent life support (PLS)

system. The e-VAD may be superior to the HVAD in terms of cost-effectiveness. It plays a role in the "double bridge" strategy when considering suitable candidates for heart transplantation and long-term management of patients with cardiogenic shock, as it is superior to p-ECMO. The objective of this study was to determine the impact of temporary e-VAD implantation as a bridge to heart transplantation.

Methods

Patients

This study was approved by the Institutional Review Board of Severance Hospital, Yonsei University College of Medicine (IRB approval no., 4-2019-0216), and informed consent was obtained. We retrospectively investigated patients who underwent e-VAD implantation between January 2018 and September 2019.

The Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) profiles of advanced heart failure were defined in the setting of a multi-institutional registry of VAD to clarify the clinical characterization of heart failure patients with a failed response to conventional treatment. INTERMACS has defined 7 clinical profiles of patients. INTERMACS profile 1 (crash and burn) patients should be considered for ECMO or percutaneous support devices [4]. Cardiogenic shock is defined as a cardiac index less than 2.0 $L/min/m^2$ with a systolic blood pressure less than 100 mm Hg, pulmonary capillary wedge pressure >20 mm Hg, and dependence on 2 or more inotropic agents with or without an intra-aortic balloon pump.

The inclusion criteria for e-VAD implantation were as follows: (1) patients with refractory cardiogenic shock and multi-organ dysfunction who were expected to be removed from the list of candidates for heart transplantation; (2) those whose LV dysfunction did not improve clinically despite more than 2 weeks of p-ECMO support; (3) those who were expected to receive p-ECMO support for more than 2 weeks because of old age, malnutrition, and severe frailty; and (4) those who had a risk of imminent death secondary to life-threatening recurrent ventricular arrhythmia or unstable angina with life-threatening coronary anatomy and severe LV dysfunction not amenable to revascularization, along with no known existing absolute contraindications to heart transplantation.

The age, sex, comorbidities, indication for e-VAD, goal of e-VAD treatment, and period from LVAD implantation to transplantation for each patient were recorded. Preoperative laboratory data, including full blood count, blood urea nitrogen, creatinine, target international normalized ratio, activated partial thromboplastin time, and activated clotting time (ACT) were collected.

The primary outcome of this study was overall survival during follow-up. The secondary outcomes were postoperative outcomes, including echocardiographic factors, such as LV end-diastolic dimension/LV end systolic dimension, and changes in the Sequential Organ Failure Assessment (SOFA) score. Additionally, we defined adverse events as including infection, pump failure, thrombosis, new-onset arrhythmia requiring pacemaker insertion, bleeding requiring re-operation, respiratory complications requiring reintubation, acute kidney injury, and cerebrovascular accident infarction.

Surgical technique

Patients underwent e-VAD implantation through a median sternotomy. These high-risk patients were usually switched to cardiopulmonary bypass (CPB) machines at the time of VAD implantation surgery. CPB has advantages such as lowering blood loss in the surgical field and facilitating adequate filling or decompression of the left ventricle (e-VAD preload). The ascending aorta and right atrium were cannulated to establish CPB. When an additional procedure, such as repair of an atrial septal defect or tricuspid valve, was required, a bicaval technique was performed for cannulation. The circuit was composed of a single centrifugal pump without an oxygenator using a PLS system from Maquet Medical Systems (Jostra Medizintechnik AG, Hirrlingen, Germany) (Fig. 1).

Two 27F venous cannulas were used to provide support. The LV apex was elevated by placing a long string underneath the heart. Double-pledgeted purse-string sutures were placed in the anterolateral aspect of the LV apex using 3-0 Prolene. The heart was then volume-loaded, and CPB flow was decreased while a cruciate incision was made in the center of the purse-string sutures. The incision was made at a distance of 1–2 cm from the lateral side of the left anterior descending course. The cannula was inserted, and rubber sliders were tightened and secured to the cannula. Cannular positioning was confirmed by intraoperative transesophageal echocardiography. If the inflow cannula was evacuated to air, it was connected to the device (Fig. 2). The cannula was then externalized subcostally. This should be done before its insertion to prevent subsequent inadvertent decannulation or tearing of the purse-

string sutures (Fig. 3).

Right ventricular (RV) failure is a leading cause of mortality after LVAD implantation. Thus, we were prepared to
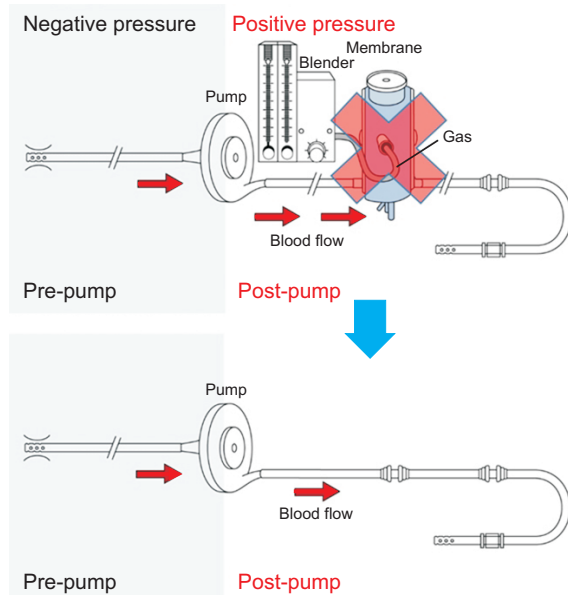
Fig. 1. The circuit of the extracorporeal ventricular assist device with a single centrifugal pump and no oxygenator using the permanent life support system from Maquet (Jostra Medizintechnik AG, Hirrlingen, Germany). The inflow cannula was inserted into the left ventricle apex, and the outflow cannula was positioned in the ascending aorta.

run temporary right-heart support using a centrifugal pump (RVAD) for RV failure via a left anterior mini-thoracotomy [5]. We performed echocardiography twice a day to evaluate severe right heart failure. The definition of severe RV failure after LVAD insertion and indications for RVAD implantation have been described elsewhere [6].

Anticoagulation protocol

Aspirin was administered on the operative day to all patients without postoperative bleeding. Anticoagulation was initiated and maintained with intravenous heparin during support under a cardiac index of 3.0 L/min. Patients with e-VAD implantation at our institution are routinely anti-coagulated using aspirin and heparin, with an ACT of 160–180 seconds. ACT was measured at 1-hour intervals on day 1 after surgery, and then measured at intervals of 4 hours.

Statistical analysis

Continuous data are presented as mean±standard deviation or as median and interquartile ranges (IQRs). Categorical variables were analyzed using the Fisher exact test, and continuous variables were evaluated using the Mann-Whitney U-test. The overall survival was estimated using Kaplan-Meier curve analysis, and differences between
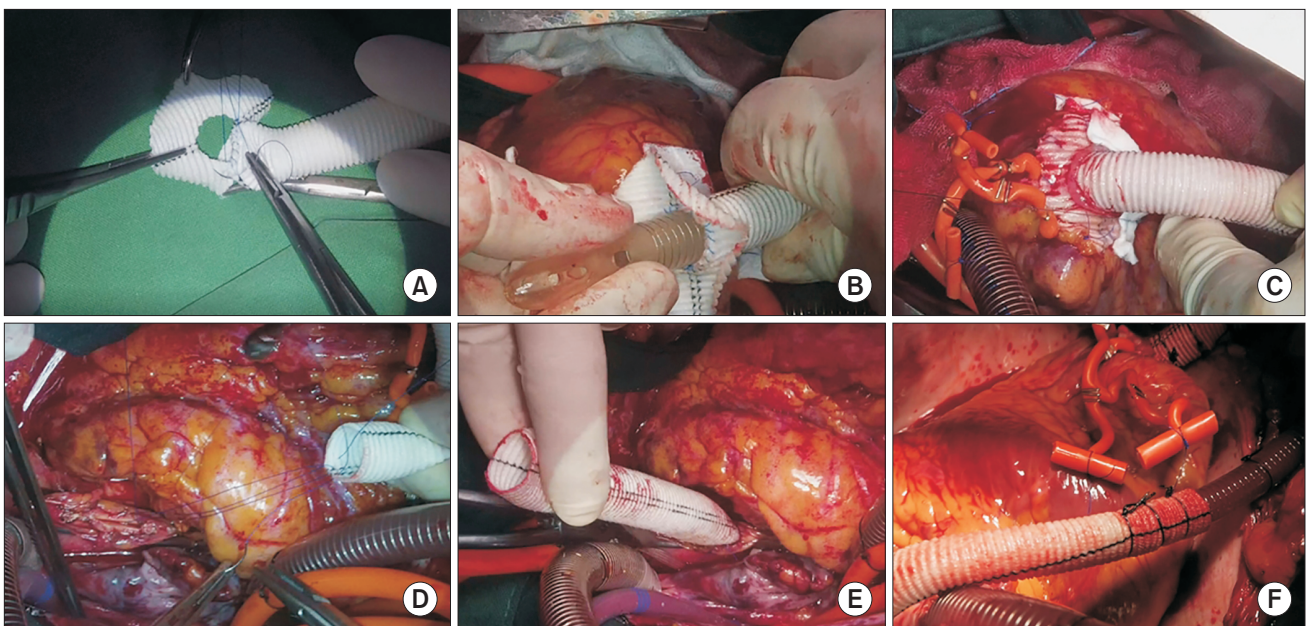
Fig. 2. (A–C) The inflow cannula was inserted into the left ventricle apex using a 27F venous cannula with a skirt made with a Hemashield 12 mm graft. (D–F) The outflow cannula was positioned in the ascending aorta using end-to-side anastomosis under partial aortic clamping with a Hemashield 12-mm graft connected by a 27F venous cannula.
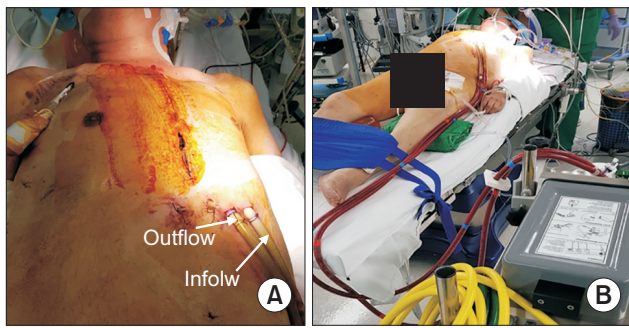
Fig. 3. (A, B) The inflow and outflow cannulae were placed through the left subcostal margin via a subcutaneous tunnel. Written informed consent for publication of this image was obtained from the patient.

Table 1. Baseline characteristics of patients

Characteristic	Value
Age (yr)	52.5
Female sex	4 (66.6)
Body surface area (m²)	1.64
Dilated cardiomyopathy	3 (50.0)
Myocarditis	2 (33.3)
Ischemic cardiomyopathy	1 (16.7)
Hypertension	2 (33.3)
Diabetes mellitus	1 (16.7)
Chronic renal failure	0
Smoking history	1 (16.7)

Values are presented as median or number (%).

Results

Six patients underwent e-VAD implantation between January 2018 and September 2019. The median follow-up duration was 8.4±6.9 months (range, 0.7–18.0 months). Patient characteristics are shown in Table 1. The median age was 52.5 years (IQR, 30.8–63.8 months), and there were more women (66.7%) than men. Half of the patients had dilated cardiomyopathy, 2 patients were diagnosed with myocarditis (33.3%), and 1 patient (16.7%) had ischemic cardiomyopathy (ICMP). Five patients (83.3%) received mechanical ventilation, and 1 (16.7%) received non-invasive ventilation preoperatively. Four patients (66.7%) had an implantable cardioverter defibrillator (ICD) or pacemaker.

We immediately placed an e-VAD directly, without bridging with ECMO, in 2 patients (33.3%). Additionally, 4 patients (66.7%) were switched to a left heart bypass circuit without an oxygenator from p-ECMO as a double bridge. In 3 patients (50.0%), renal failure was treated using a continuous renal replacement therapy (CRRT) device preoperatively (Table 2).

In all patients, emergency or urgent surgery was performed. Three patients underwent concomitant procedures, including atrial septal defect repair (n=2) and tricuspid valve repair (n=1). The mean aortic cross-clamping time was 92.2±8.5 minutes, and the mean CPB time was 158.6±15.0 minutes.

After e-VAD implantation, all patients received inotropic support during the first few days, and most patients (83.3%) were weaned from inotropics 2.3±1.7 days after device implantation. Extubation was successfully carried out in 3 patients (50.0%) and O$_2$ demand was minimized in 2 patients (33.3%). The e-VAD affected the fraction of inspired oxygen (FiO$_2$) in all patients, and FiO$_2$ significantly decreased postoperatively (p=0.035) (Table 3).

After surgery, 66.7% of the patients who initially received CRRT (2 of 3) had improved renal function and remained free of CRRT. On echocardiography, the left atrial volume index and the LV end diastolic diameter showed a tendency to decrease; however, the difference was not significant (p=0.780 and p=0.311, respectively). The SOFA scores significantly decreased from 8.7±3.6 to 4.3±3.1 (p=0.048). Recovery of multi-organ function was seen, and bedside rehabilitation was initiated in 5 patients (83.3%). There were no cases of postoperative hemorrhagic complications requiring re-operation, new-onset arrhythmia, re-intubation, and/or wound dehiscence after e-VAD.

After e-VAD support for a mean duration of 14.5±17.3 days (range, 2–48 days), all patients were successfully bridged to transplantation. The mean time from listing to transplantation was 45.2±32.9 days (range, 15–92 days). During the follow-up period after transplantation, respiratory failure requiring re-intubation occurred in 2 patients (33.3%). One patient (16.7%) required CRRT due to new-onset renal failure. One 49-year-old male patient died on postoperative day 13 due to septic shock caused by pneumonia. The patient had ICMP with an ICD device. In Kaplan-Meier analysis, the 6-month survival rate was 83.3% (Fig. 4).

Discussion

In this study, we demonstrated that e-VAD can provide

Table 2. Individual case details

No.	Age (yr)	Sex	Height (cm)	Weight (kg)	BSA (m²)	Diagnosis	NYHA class	Medical history	Prior cardiac surgery	CPR before a-VAD	Mechanical ventilation	ICD/PM implantation	Prior p-ECMO	Duration of p-ECMO support (day)	Duration of a-VAD support (day)	Waiting time for HTX (day)
1	49	M	169	83	1.97	ICMP	IV	CAOD 3vd after PCI, Afib, DM, alcoholism	N	N	N	Y	N	-	9	60
2	32	F	168	66	1.75	DCMP	IV	Breast cancer after MRM, neoadjuvant CTx	N	Y	Y	N	Y	3	2	19
3	27	F	164	50	1.52	Myocarditis	IV	None	N	N	Y	N	Y	13	2	16
4	56	M	163	79	1.89	DCMP	IV	HTN, CAOD 3vd, Afib, CKD, hypothyroidism	N	N	Y	Y	N	-	17	69
5	72	F	150	44	1.36	DCMP	IV	HTN, DM, Afib, CKD, old CVA	N	N	Y	Y	Y	13	48	92
6	61	F	152	48	1.43	Myocarditis	IV	Post-cholecystectomy	N	N	Y	Y	Y	5	9	15

BSA, body surface area; NYHA, New York Heart Association; CPR, cardiopulmonary resuscitation; a-VAD, assembled ventricular assist device; ICD, implantable cardioverter defibrillator; PM, pacemaker; p-ECMO, peripheral extracorporeal membrane oxygenation; HTX, heart transplantation; M, male; F, female; ICMP, ischemic cardiomyopathy; CAOD 3vd, coronary artery occlusive disease in 3 vessels; PCI, percutaneous coronary intervention; Afib, atrial fibrillation; DM, diabetes mellitus; N, no; Y, Yes; DCMP, dilated cardiomyopathy; MRM, modified radical mastectomy; CTx, chemotherapy; HTN, hypertension; CKD, chronic kidney disease; CVA, cerebrovascular accident.

LV unloading and circulatory support for patients with INTERMACS profile 1. The success rate of bridging to transplantation in this cohort of 6 patients was 100%. Pump performance data indicated satisfactory hemodynamic support that was sufficient to meet the shock patients' circulatory needs. The benefits associated with e-VAD include ease of implantation, adequate ventricular unloading, reliable device function, no requirement for prior approval, and a low incidence of device-related complications compared to p-ECMO. The 6-month survival of these patients was 83.3%; thus, these outcomes support conditions conducive to recovery from cardiogenic shock.

Despite many advances in the management of patients with acute heart failure, the outcomes for patients with refractory acute cardiogenic shock remain poor [7,8]. Furthermore, in the Republic of Korea, these patients do not have access to advanced circulatory support technologies or the resources to manage them because there is no available temporary e-VAD device on the market. Delay in referral to tertiary centers further exacerbates the poor outcomes in this group of patients. Therefore, there is a need for the wider application of temporary circulatory support in such patients.

The primary hemodynamic goals of e-VAD are to decrease the preload, decrease the afterload, and augment the cardiac output. The end goal is to provide adequate organ perfusion and oxygen delivery, which can bridge patients to recovery or a more durable device, and can also support them through high-risk procedures [9,10]. Temporary e-VAD can be used to mechanically unload the LV with concomitant ECMO to replace pulmonary gas exchange. However, ECMO does not unload the ventricles to the degree possible with an LVAD and has a high rate of device-related complications [11]. Moreover, ECMO requires the patient to be immobilized. Other commercially available extracorporeal devices have major disadvantages, such as a large priming volume, limited duration of use, thromboembolic risk, and device size [12-14]. This study highlights the recovery of organ dysfunction and ambulation after e-VAD, with implications for the selection of the best short-term circulatory assist system for acute cardiogenic shock or while sliding on inotropes.

Kashiwa et al. [15] reported a case in which left heart bypass support with the Rotaflow centrifugal pump was performed as a bridge to transplantation decision and recovery. Of note, the pump could be used continuously for more than 30 days [15]. In the present study, e-VAD was used as a bridge to transplantation in a 72-year-old female patient for 48 days. e-VAD has the potential advantage of

Table 3. Procedure-related details and changes in hemodynamic/laboratory parameters after assembled extracorporeal VAD

Characteristic	Preoperative	Postoperative	p-value
LVEF (%)	20.2±10.7	20.7±9.1	0.899
LAVI (mL/m²)	64.1±32.7	56.6±31.8	0.780
LVEDD (mm)	62.7±13.6	57.2±14.8	0.311
LVESD (mm)	55.5±15.1	52.2±17.8	0.506
RVSP (mm Hg)	46.5±19.6	42.3±8.4	0.812
Blood urea nitrogen (mg/dL)	26.5±17.5	31.2±24.2	0.433
Creatinine (mg/dL)	0.9±0.3	0.9±0.4	0.409
Glomerular filtration rate (MDRD)	77.0±22.0	57.5±26.1	0.311
Total bilirubin (mg/dL)	17.8±23.7	2.4±0.8	0.172
AST (IU/L)	138.7±196.9	71.0±74.6	0.696
ALT (IU/L)	136.3±45.2	44.5±45.2	0.355
Amylase (U/L)	68.5±36.7	89.3±51.8	0.415
Lipase (U/L)	121.0±118.8	66.5±56.3	0.086
Lactate (mmol/L)	2.0±1.2	2.0±1.1	0.697
LDH (IU/L)	2,457.7±220.8	671.3±32.5	<0.001
PT (INR)	1.2±0.2	1.3±0.1	0.999
SOFA score	8.7±3.6	4.3±3.1	0.048
PaO₂ (mm Hg)	146.9±85.6	186.8±55.9	0.425
FiO₂ (%)	70.0±32.9	30.0±8.9	0.035
On mechanical ventilation	5 (83.3)	2 (33.3)	0.180
Platelets (10³/μL)	112.7±34.7	140.2±64.0	0.403
Glasgow Coma Scale	12.2±1.8	13.7±2.1	0.304
Bilirubin (mg/dL)	6.9±13.0	2.5±0.7	0.047
Administration of vasoactive agents required	6 (100.0)	1 (16.7)	0.025
Continuous renal replacement therapy	3 (50.0)	1 (16.7)	0.157

Values are presented as mean±standard deviation or number (%).
VAD, ventricular assist device; LVEF, left ventricular ejection fraction (%); LAVI, left atrial volume index (mL/m²); LVEDD, left ventricular end-diastolic dimension (mm); LVESD, left ventricular end systolic dimension (mm); RVSP, right ventricular systolic pressure; MDRD, Modification of Diet in Renal Disease; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; PT, prothrombin time; INR, international normalized ratio; SOFA, Sequential Organ Failure Assessment; PaO₂, partial pressure of oxygen; FiO₂, fraction of inspired oxygen.
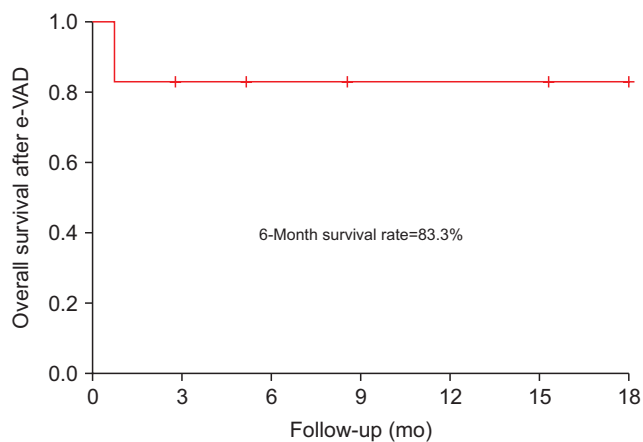
Fig. 4. Kaplan-Meier survival analysis of e-VAD implantation. e-VAD, extracorporeal ventricular assist device.

serving as a bridge to long-term support in patients who continue to have unresolved end-organ dysfunctions during ECMO support. Thus, we demonstrated that e-VAD can be used as a durable long-term device for patients awaiting transplantation.

ECMO is well known to result in coagulopathy, continuous activation of the contractile and fibrinolytic systems by the circuit, and consumption and dilution of factors. This occurs within minutes of initiation of ECMO. However, systemic heparinization is still advisable because due to the risk of end-organ damage from microthrombus and fibrin deposition [16]. Moubarak et al. [17] reported a massive intraventricular thrombus in a patient on ECMO under heparinization, and thrombus formation may be increased by the unloading of cardiac chambers observed with LVADs. Thus, we provided our patients with low levels of heparin and aspirin to prevent clotting of both cannulae, tubing, and the bearing of the centrifugal pump. In this study, no thrombus formation was found in the cannula and circuit tube. Heparin and concurrent use of an antiplatelet agent (aspirin) might be considered to further prevent thrombus formation. Furthermore, a simple circuit configuration

without branches may also help prevent thrombus formation.

The present study has several limitations. First, a major limitation of this study is the relatively small sample size. Second, this study was a retrospective analysis of observational data. Third, the study population did not include a control group. Lastly, there remains potential variation among patients regarding antibiotic protocols and the management of postoperative complications.

We have demonstrated that e-VAD using an assembled PLS circuit can provide effective LV support for patients with medically refractory acute cardiogenic shock to optimize heart transplantation with acceptable survival.

Conflict of interest

Acknowledgments

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