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ORIGINAL ARTICLE

Artificial Heart (Clinical)

Temporary biventricular support with extracorporeal membrane oxygenation: a feasible therapeutic approach for cardiogenic shock with multiple organ failure

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Abstract Various strategies using a ventricular assist device (VAD) are applied to rescue Interagency Registry for Mechanically Assisted Circulatory Support profile 1 (Profile-1) patients. However, the optimal use of VAD in Profile-1 patients has not been completely elucidated. We retrospectively reviewed 23 Profile-1 patients [mean age 36.9 ± 16.6 years, 14 males; 11 with non-ischemic cardiomyopathy (NICM), 9 with fulminant myocarditis (FM), 2 with ischemic cardiomyopathy (ICM), and 1 with peripartum cardiomyopathy (PPCM); 18 with pre-operative percutaneous extracorporeal membrane oxygenation (p-ECMO) support] who underwent VAD implantation from 2011 to 2015 at our institution. Nine initially received left VAD (LVAD) alone (NICM in 9, ICM in 2 with ICM, and FM in 1), one with NICM received biventricular VAD (BiVAD; $n = 1$), and 10 received LVAD combined with right ventricular support using an ECMO circuit (BiVAD-ECMO) (FM in 8, NICM in 1, and PPCM in 1). Paracorporeal VAD was used in all patients. ECMO was used for the patients with severe pulmonary edema, inflammation, anemia, and thrombopenia. The BiVAD patient died 1.4 months after VAD implantation. The overall survival was comparable between patients with BiVAD-ECMO and LVAD (2-year survival, 80.0 and 75.0%, respectively). Three VAD strategies were initially applied in Profile-1 patients. Among them, the BiVAD-ECMO strategy is a promising therapeutic option to rescue Profile-1 patients with multiple organ failure.

Keywords Ventricular assist device · Cardiogenic shock · INTERMACS profile 1 · Extracorporeal membrane oxygenation

Introduction

The ventricular assist device (VAD) is an alternative therapy for patients with advanced heart failure (HF) who do not respond to conventional guideline-directed HF therapies [1–3]. An increasing number of patients with advanced HF are fortunate enough to receive VAD therapy, and continuous accumulation of data from patients with VADs has generated a large body of valuable information for clinical practice. The Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) patient profiles were developed based on an analysis of post-market clinical databases of VAD therapy, which stratified patients with advanced HF in detail according to their severity. Patients with INTERMACS profile 1 (Profile-1) were recognized as the highest risk cohort for poorer prognosis after VAD implantation [4]. Consequently, cardiologists have preferred to refer advanced HF patients at higher INTERMACS profiles, such as 2, 3, or recently even higher, for VAD therapy [5, 6]. However, there are a substantial number of Profile-1 patients with various etiologies, and a range of therapeutic strategies apart from simple VAD implantation to the left ventricle is required to rescue

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them. However, the optimal VAD strategy for Profile-1 patients has not been completely elucidated. In this study, we aimed to clarify the optimal use of VAD in Profile-1 patients by analyzing the 4-year experience of VAD usage at our institution.

Methods

Patient population

We retrospectively reviewed 90 consecutive patients with advanced HF who received VADs between April 2011 and October 2015 at the National Cerebral and Cardiovascular Center. All patients received VAD implantation for bridge to transplant (BTT), bridge to transplant candidacy, or rescue therapy including bridge to recovery (BTR), and were followed up until December 2015. Among them, 23 Profile-1 patients at the time of VAD implantation were enrolled for the analysis. Data collection, analysis, and reporting were approved by the National Cerebral and Cardiovascular Center Institutional Review Board.

Clinical parameters

Patients' medical records were reviewed retrospectively for baseline clinical parameters, including demographics (age, sex, body mass index, body surface area, duration of HF, etiology, and HF treatments prior to VAD implantation), blood examination results (white blood cell count, hemoglobin, albumin, total bilirubin, creatinine, blood urea nitrogen, serum sodium, C-reactive protein, brain natriuretic peptide), and echocardiographic parameters [left ventricular diastolic dimension (LVDd), left ventricular systolic dimension, ejection fraction, interventricular septal thickness (IVST), and posterior wall thickness]. The severity of each patient's disease was stratified according to INTERMACS profile.

Therapeutic strategies for patients with INTERMACS profile 1

For Profile-1 patients, only paracorporeal devices, such as Nipro-Toyobo VAD (Nipro-VAD; Nipro, Osaka, Japan) and AB5000 (Abiomed, Inc., Danvers, MA, USA), have been approved for clinical use in Japan by the national health insurance authority. We commonly use Nipro-VAD. The surgical procedure for VAD implantation into the left ventricle (LV) has been described in previous reports [7, 8]. Our basic therapeutic strategies for rescue therapy using VAD, according to patients' disease conditions, are as follows:

1. A left VAD (LVAD) alone was implanted in cases with predominant LV dysfunction and preserved right ventricular (RV) function without severe pulmonary edema.
2. Biventricular VADs (BiVAD) were implanted in cases with severe bilateral ventricular dysfunction. The decision to perform right VAD (RVAD) implantation was made based on pre-operative and perioperative findings. Pre-operatively, echocardiographic visual and objective findings, such as enlargement of the RV with reduced contraction and tricuspid annual plane systolic excursion <10 mm, are strongly suggestive of the necessity for RVAD. During the operation, after LVAD implantation, in the event of persistent elevation of central venous pressure >15 mmHg and/or collapse of the left ventricle including abnormal septal shift to the RV while weaning off of cardiopulmonary bypass (CPB), RVAD is considered for implantation. For RVAD implantation, the inflow cannula is generally placed in the apex of the RV, and the outflow graft is anastomosed to the main pulmonary artery (main PA).
3. In cases with RV failure and severe respiratory failure due to pulmonary edema, an extracorporeal membrane oxygenation (ECMO) circuit is initially used for RV support in addition to LVAD (BiVAD-ECMO). Our RV support system using the ECMO circuit (RVAD-ECMO) was previously described [9]. Briefly, RVAD-ECMO was established using an extracorporeal life support system (Endumo® 6000; Heiwa Bussan, Tokyo, Japan), which consists of a ROTAFLOW® centrifugal pump (Maquet, Rastatt, Germany) and a circuit (T-NCVC coating; National Cardiovascular Center, Osaka, Japan), and an oxygen membrane (BIOCUBE® 6000; Nipro, Osaka, Japan). The decision to perform BiVAD-ECMO implantation was made based on the following findings in addition to the criteria for BiVAD described above. If massive pulmonary edema is revealed pre-operatively on chest X-ray and/or computed tomography, or if there is a severe decrease in the ratio of arterial oxygen partial pressure to fractional inspired oxygen while weaning off CPB, BiVAD-ECMO is considered. Two surgical procedures were commonly applied in the RVAD-ECMO system. First, the inflow cannula of the CPB (DLP right angle metal tip venous cannulae; Medtronic, Inc., Minneapolis, MN, USA) placed in the inferior vena cava is kept in place and used as the inflow cannula of the RVAD-ECMO, and the 18-Fr outflow cannula (OptiSite; Edwards Lifesciences, Irvine, CA, USA) is placed in the main PA and fixed with double purse string suture. Second, the inflow cannula (Bio-Medicus™ NextGen venous femoral

Cannulae; Medtronic, Inc., Minneapolis, MN, USA) is placed in the femoral vein, and the 18-Fr outflow cannula (OptiSite) is placed in the main PA through an 8-mm-diameter synthetic graft (Hemashield Platinum grafts, intervascular; La Ciotat, France), which is end-to-side anastomosed to the main PA and led out from the left second intercostal space. The first procedure facilitates physical rehabilitation of patients even on RVAD-ECMO support, whereas the second procedure removes the RVAD-ECMO system without open-heart surgery.

If respiratory function and native cardiac function recover after VAD implantation, each VAD is removed in a staged manner from RVAD to LVAD. With regard to weaning of the RVAD-ECMO system, hemodynamic evaluation during temporary suspension of the RVAD-ECMO system (RVAD off test) was performed within 2 weeks after VAD implantation. If systemic circulation, which was comprehensively assessed using arterial blood pressure, echocardiography (LVDd and velocity–time integral of RV outflow), parameters of right heart catheterization (pulmonary artery pressure, right atrial pressure, and cardiac output), and flow volume of LVAD, was maintained during RVAD off test, the RVAD-ECMO system was removed. LVAD with veno-venous ECMO is a therapeutic option for patients with prolonged respiratory failure with recovered RV function. If circulatory collapse was observed during the RVAD off test, the RVAD-ECMO system was converted to the durable RVAD system using Nipro-VAD. In such cases, the outflow cannula was anastomosed to the main PA, and the inflow to the RV apex. If the patient's native cardiac function does not recover, candidacy for heart transplantation is assessed, and a conversion from Nipro-LVAD to an implantable continuous-flow LVAD (CF-LVAD) is considered after the patient has been determined as a candidate for heart transplantation (bridge to bridge, BTB). No patients with BiVAD-ECMO required persistent RV support by implantable device when they underwent CF-LVAD implantation.

Statistical analysis

Continuous variables are expressed as mean ± standard deviation (SD) or as median (interquartile range), as appropriate. The 2 groups were compared using an unpaired t test for data with normal distribution or Mann–Whitney U test for data without normal distribution. Categorical variables are expressed as numbers and frequencies. The Chi-square test was used for categorical variables. Kaplan–Meier analysis and log-rank test were used to evaluate overall survival. All p values are two sided, and values of $p < 0.05$ were considered significant. Statistical analysis was performed using JMP software (version 10; SAS institute Inc., USA).

Results

Distribution, VAD strategy, and clinical outcome of patients with INTERMACS profile 1

The baseline characteristics of Profile-1 patients are presented in Table 1. Profile-1 patients included not only those with worsening of chronic HF but also those with de novo acute cardiogenic shock due to acute myocardial infarction (AMI, $n = 1$), fulminant myocarditis (FM, $n = 9$), and peripartum cardiomyopathy (PPCM, $n = 1$). Figure 1a is the flow diagram of the analysis of patients with VAD. Of the 90 patients, 23 (26%) were Profile-1, while 22 (24%) and 45 (50%) patients were Profile-2 and Profile-3, respectively. Of the 23 Profile-1 patients, 18 had been supported by percutaneous veno-arterial extracorporeal membrane oxygenation (p-ECMO) just before LVAD implantation. Only one female patient with fulminant myocarditis was already beyond the age limit for heart transplantation at the time of VAD implantation and she did not have a choice for BTT, but only for BTR. Twelve Profile-1 patients underwent LVAD implantation alone, one underwent BiVAD implantation, and 10 underwent BiVAD-ECMO implantation (Fig. 1a). Profile-1 patients were followed up for a mean of 642 days (range 15–1698 days) after initial VAD implantation. During the follow-up period, 2 patients with FM and 1 patient with PPCM were successfully weaned from VAD and had a favorable course. Twelve of fourteen patients who could not be weaned from a LVAD were successfully converted to an implantable CF-LVAD. Four patients, including 3 BTB cases, successfully underwent heart transplantation during the follow-up period. Ten patients, including 9 BTB cases, are still supported by VAD and waiting for heart transplantation. Six Profile-1 patients died within 90 days after VAD implantation, and the 2-year survival rate of Profile-1 patients was 73.9%, which was significantly inferior to that of Profile-2 and Profile-3 patients (with 2-year survival rates of 95.5 and 97.3%, respectively, $p = 0.007$, log-rank test) (Fig. 1).

BiVAD-ECMO strategy for critically ill patients complicated by respiratory failure

Table 1 also shows the pre-operative clinical characteristics of the patients stratified according to VAD strategy. Statistical comparisons were made between patients with LVAD and those with BiVAD-ECMO. Patients with BiVAD-ECMO were found to have a shorter duration of

Table 1 Baseline pre-operative characteristics

	Overall $n = 23$	LVAD alone $n = 12$	LVAD with pre-ECMO $n = 7$	BiVAD-ECMO $n = 10$	BiVAD $n = 1$	p value LVAD vs BiVAD-ECMO	p value LVAD with pre-ECMO vs BiVAD-ECMO
Age (years)	36.9 ± 16.6	35.0 ± 16.2	37.1 ± 16.7	37.9 ± 18.3	49	0.71	0.93
Male sex [*n* (%)]	14 (60.9)	8 (66.7)	4 (57.1)	6 (60)	Female	0.74	0.91
Body mass index	21.3 ± 3.5	21.6 ± 3.5	22.7 ± 4.0	21.2 ± 3.6	18.8	0.78	0.43
Body surface area (m^2)	1.6 ± 0.2	1.6 ± 0.2	1.7 ± 0.3	1.6 ± 0.2	1.4	0.93	0.67
Duration of heart failure (days)	47 (5, 996)	534 (26, 1820)	996 (7, 2075)	6 (4, 26)	3352	0.008	0.06
Etiology [*n* (%)]							
DCM	8 (de novo DCM, $n = 1$)	7	3	1	0		
dHCM	3	2	2	0	1		
Fulminant myocarditis	9	1	1	8	0		
ICM	2 (AMI, $n = 1$)	2	1	0	0		
PPCM	1	0	0	1	0		
Pre-VAD MCS [*n* (%)]							
p-ECMO	18 (78.3)	7 (58.3)	7 (100)	10 (100)	1	0.02	–
Duration of p-ECMO (days)	3.5 (1, 6)	2 (1, 6)	2 (1, 6)	4.5 (1.8, 7)	1	0.23	0.23
IABP	22 (95.7)	12 (100)	7 (100)	9 (90)	1	0.26	0.29
Pre-VAD ventilation [*n* (%)]	19 (82.6)	8 (66.7)	6 (85.7)	10 (100)	1	<0.05	0.17
Medication [*n* (%)]							
β-Blocker	10 (43.5)	9 (75.0)	6 (85.7)	1 (10)	0	0.002	0.001
ACE inhibitor or Ang II antagonist	6 (26.1)	5 (41.6)	3 (42.9)	1 (10)	0	0.09	0.11
Aldosterone antagonist	8 (34.8)	7 (58.3)	4 (57.1)	1 (10)	0	0.02	0.03
Laboratory examinations							
White blood cell count (/μL)	9978 ± 4889	7950 ± 3080	8657 ± 3857	12,980 ± 5268	4300	0.01	0.08
Hemoglobin (mg/dL)	10.5 ± 1.9	11.3 ± 1.9	10.7 ± 1.5	9.7 ± 1.4	9.4	0.03	0.19
Platelets (×10,000/μL)	8.7 (6.1, 12.6)	10.6 (8.6, 17.8)	9.9 (8.8, 15.7)	6.1 (4.8, 8.5)	11.7	0.008	0.03
Albumin (mg/dL)	3.1 ± 0.5	3.2 ± 0.1	3.1 ± 0.5	2.8 ± 0.4	3.5	0.05	0.22
Total bilirubin (mg/dL)	4.7 ± 3.2	3.6 ± 2.8	4.1 ± 3.4	6.2 ± 3.2	1.7	0.06	0.21
Creatinine (mg/dL)	1.4 ± 1.1	1.1 ± 0.5	1.3 ± 0.6	1.6 ± 1.6	1.6	0.33	0.59
Blood urea nitrogen (mg/dL)	34.7 ± 22.1	29.5 ± 17.3	27.0 ± 15.4	38.2 ± 26.4	61	0.36	0.33
Serum sodium (mEq/L)	138.8 ± 7.1	140.2 ± 5.9	142.6 ± 5.0	139.1 ± 2.3	119	0.68	0.23
C-reactive protein (mg/dL)	6.5 (2.9, 19.5)	4.7 (2.7, 6.4)	6.3 (4.5, 14.9)	19.0 (9.4, 34.2)	0.72	0.005	0.05
Brain natriuretic peptide (pg/ml)	713 (364, 1480)	1139 (407, 1887)	537.4 (278.7)	604 (314, 905)	852	0.25	0.96

Table 1 continued

	Overall	LVAD alone	LVAD with pre-ECMO	BiVAD-ECMO	BiVAD	*p* value		*p* value
	$n = 23$	$n = 12$	$n = 7$	$n = 10$	$n = 1$	LVAD vs BiVAD-ECMO		LVAD with pre-ECMO vs BiVAD-ECMO
Echocardiographic parameters								
LV end-diastolic dimension (mm)	61.6 ± 15.2	70.4 ± 13.3	66.3 ± 15.8	53.3 ± 10.4	38	0.004		0.06
LV end-systolic dimension (mm)	57.1 ± 15.6	65.3 ± 13.4	61.4 ± 15.9	50.2 ± 11.8	28	0.01		0.11
IVST (mm)	7.9 ± 2.1	6.9 ± 1.7	7.3 ± 2.1	8.9 ± 2.2	9	0.03		0.15
PWT (mm)	8.1 ± 2.4	7.3 ± 2.1	7.6 ± 1.8	9.2 ± 2.6	8	0.06		0.18
LV ejection fraction (%)	12.5 ± 10.1	11.3 ± 3.2	9.6 ± 3.1	9.9 ± 5.2	55	0.45		0.9

DCM dilated cardiomyopathy, *dHCM* dilated-phase hypertrophic cardiomyopathy, *ICM* ischemic cardiomyopathy, *PPCM* peripartum cardiomyopathy, *MCS* mechanically circulatory support, *p-ECMO* percutaneous extracorporeal membrane oxygenation, *IABP* intra-aortic balloon pumping, *ACE* angiotensin-converting enzyme, *Ang* angiotensin, *LV* left ventricular, *IVST* interventricular septal thickness, *PWT* posterior wall thickness

HF [6 (4, 26) days vs. 534 (26, 1820) days, $p = 0.008$], a higher rate of pre-operative p-ECMO support (100 vs. 58.3%, $p = 0.02$), and more critical conditions, such as inflammation [WBC: 12,980 ± 5268/μL vs. 7950 ± 3080/μL, $p = 0.01$; C-reactive protein: 19.0 (9.4, 34.2) mg/dL vs. 4.7 (2.7, 6.4) mg/dL, $p = 0.005$], anemia (hemoglobin: 9.7 ± 1.4 vs. 11.3 ± 1.9 mg/dL, $p = 0.03$), and thrombocytopenia [platelets: 6.1 (4.8, 8.5)*10,000/μL vs. 10.6 (8.6, 17.8)*10,000/μL]. End-organ failure (total bilirubin: 6.2 ± 3.2 vs. 3.6 ± 2.8 mg/dL, $p = 0.06$) and low nutrition (albumin: 2.8 ± 0.4 vs. 3.2 ± 0.1 mg/dL, $p = 0.05$) tended to be more prevalent in patients with BiVAD-ECMO compared to those with LVAD alone. A smaller LV and thicker interventricular wall were also found in patients with BiVAD-ECMO (LVDd: 53.3 ± 10.4 vs. 70.4 ± 13.3 mm, $p = 0.02$; IVST, 8.9 ± 2.2 vs. 6.9 ± 1.7 mm, $p = 0.04$). Since the presence or absence of pre-operative p-ECMO support may have an effect on post-operative course, patients with LVAD alone who had been supported with pre-operative p-ECMO (LVAD with pre-ECMO, $n = 7$) and patients with BiVAD-ECMO (all patients had received p-ECMO pre-operatively) were compared, and the results indicated a similar tendency. After VAD implantation, patients with BiVAD-ECMO required a longer operative time and higher transfusion volume compared to those with LVAD (Table 2). Longer duration of ventilation, longer intensive care unit (ICU) stay, and higher rate of hemodialysis were observed in patients with BiVAD-ECMO. Patients with BiVAD-ECMO required a median value of 11.5 days of RVAD support (range 4–167 days). Among the 8 patients with BiVAD-ECMO who survived, 5 [1 with PPCM, 1 with dilated cardiomyopathy (DCM), and 3 with FM] required about a week of RVAD support (5, 4, 5, 6, and 8 days, respectively), whereas 3 patients with FM underwent conversion from RVAD-ECMO to durable RVAD support using Nipro-VAD, and required more than 2 months of RVAD support (80, 167, and 173 days, respectively). Six cases died within 90 days after VAD implantation (Table 3). Although the more critical pre- and post-operative conditions were found in patients with BiVAD-ECMO, overall survival was comparable between patients with BiVAD-ECMO and those with LVAD (2-year survival, 80.0 and 75.0%, respectively, $p = 0.82$, log-rank test) (Fig. 2). The patient with BiVAD died on BiVAD support 1.4 months (42 days) after VAD implantation.

Discussion

Currently, VAD therapy is recognized as established therapy for patients with advanced HF, and its use is increasing globally because of its likelihood of achieving a favorable

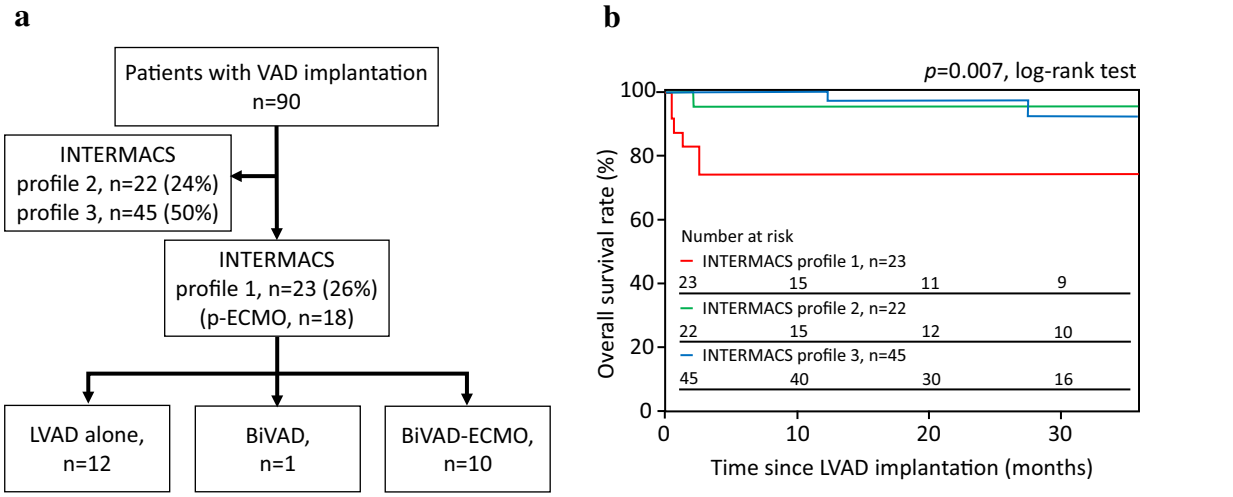

Fig. 1 Overview of enrolled patients and Kaplan–Meier curves for overall survival. This flowchart shows the incidence and therapeutic strategies for patients classified as INTERMACS profile 1 (**a**). The 2-year overall survival rate of Profile-1 patients was significantly inferior to that of Profile-2 and Profile-3 patients (73.9 vs. 95.5 and 97.3%, respectively, $p = 0.007$, log-rank test) (**b**). *LVAD* left ventricular assist device, *p-ECMO* percutaneous extracorporeal membrane oxygenation, *BiVAD* biventricular assist device, *RVAD* right ventricular assist device, *DCM* dilated cardiomyopathy, *dHCM* dilated-phase hypertrophic cardiomyopathy, *ICM* ischemic cardiomyopathy, *PPCM* peripartum cardiomyopathy

Table 2 Post-operative outcomes stratified by VAD strategies

	Overall $n = 23$	LVAD alone $n = 12$	BiVAD-ECMO $n = 10$	BiVAD $n = 1$	p value LVAD vs BiVAD-ECMO
Operative time (min)	276 ± 68	263 ± 87	290 ± 33	830	0.37
Nitric oxide therapy [*n* (%)]	18 (78.2)	10 (83.3)	8 (80)	0	0.84
Tricuspid annuloplasty [*n* (%)]	3 (13)	3 (25)	0 (0)	0	0.09
Transfusion of blood products					
Packed red cell (units)	7.9 ± 6.0	5.3 ± 5.5	11.0 ± 5.1	68	0.02
Platelet concentrate (units)	36.8 ± 15.0	29.2 ± 11.2	46.0 ± 14.1	90	0.005
Fresh frozen plasma (units)	15.0 ± 10.2	9.6 ± 5.1	21.4 ± 11.2	64	0.004
Duration of ventilation (days)	3.5 (1.7, 21.5)	2.0 (1.0, 2.8)	24 (12.8, 47.8)	49	<0.001
Intensive care unit stay (days)	13 (5, 29)	5.5 (4.3, 7.0)	26 (16.8, 34.8)	40	<0.001
Post-operative hemodialysis [*n* (%)]	9	1	7	1	0.003
Major bleeding [*n* (%)]	9	3	6	0	0.09
Duration of RVAD support (days)	15 (5, 84)	–	11.5 (5, 104.8)	42	–
Hospital stay (days), $n = 15$	172 ± 63	140 ± 30	200 ± 72	–	0.06
Clinical course					
Bridge to bridge therapy [*n* (%)]	12 (52)	7	5	0	
BTT on paracorporeal VAD [*n* (%)]	2 (8.7)	2	0	0	
Successful weaning from VAD [*n* (%)]	3 (13)	2	4	0	
Death [*n* (%)]	6 (26)	3	2	1	

LVAD left ventricular assist device, *BiVAD* biventricular assist device, *BiVAD-ECMO* biventricular support using ECMO circuit for right ventricular support, *BTT* bridge to transplantation, *VAD* ventricular assist device

outcome. However, in Profile-1 patients, any therapies—including VAD therapy—can be challenging. The INTERMACS annual report clearly demonstrated that Profile-1 classification was associated with a poor prognosis after VAD implantation, inferior to that of patients with higher INTERMACS profiles. Consequently, an

Table 3 Summary of patients with early post-operative death

Age (years)	Sex	Etiology	Duration of p-ECMO (days)	Pre-operative parameters		Initial strategy of VAD	Duration of VAD support (days)	Duration of survival (days)	Cause of death
				T-Bil (mg/dL)	Cre (mg/dL)				
49	Female	dHCM	1	1.7	1.61	BiVAD	42	42	Sepsis
22	Female	dHCM	3	5	2.25	LVAD alone	16	16	Sepsis
62	Male	ICM (AMI)	2	0.8	1.3	LVAD alone	12	21	Stroke
58	Female	Full myocarditis	6	11.1	0.77	LVAD alone	16	80	Sepsis
69	Female	Full myocarditis	4	9.6	2.48	BiVAD-ECMO	15	15	MOF
61	Male	Full myocarditis	9	4.7	1.36	BiVAD-ECMO	37	79	MOF

VAD ventricular assist device, *dHCM* dilated-phase hypertrophic cardiomyopathy, *ICM* ischemic cardiomyopathy, *AMI* acute myocardial infarction, *Full myocarditis* fulminant myocarditis, *p-ECMO* percutaneous extracorporeal membrane oxygenation, *T-Bil* total bilirubin, *Cre* creatinine, *BiVAD* biventricular assist device, *LVAD* left ventricular assist device, *MOF* multiple organ failure

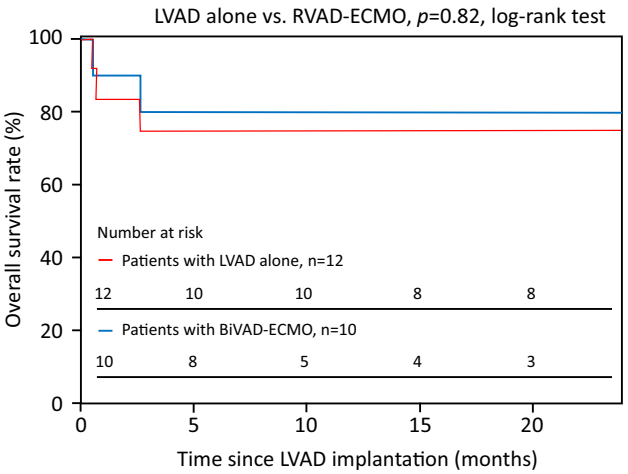

Fig. 2 Kaplan–Meier curves for overall survival stratified by therapeutic strategies for VAD. The 2-year overall survival rate was comparable between patients treated with BiVAD-ECMO and those treated with LVAD (80.0 and 75.0%, respectively, $p = 0.82$, log-rank test). *LVAD* left ventricular assist device, *BiVAD-ECMO* biventricular support using extracorporeal membrane oxygenation circuit for right ventricular support

implantable CF-LVAD is not indicated for Profile-1 patients in Japan, not only because of prognosis but also on a cost–benefit basis.

Our study offers two important pieces of clinical information related to advanced HF care. First, this report discloses the current "real-world" status of advanced HF care, in terms of the incidence and etiology of Profile-1 patients, in addition to the outcomes of these patients. Our results show that the incidence of Profile-1 patients in our institution remained high compared with that in the INTERMACS annual report, as 26% of patients who received VAD implantation were of Profile-1. Half of our Profile-1 patients had a disease with an acute-onset etiology, such as FM ($n = 9$), AMI of the left main trunk ($n = 1$), PPCM ($n = 1$), or de novo DCM ($n = 1$), with a short duration of HF. Therefore, it was unavoidable for these patients to undergo VAD implantation under Profile-1 status. With respect to the outcome of Profile-1 patients, their 2-year survival rate was 73.9%, which is comparable to that of the INTERMACS annual report. Considering that paracorporeal VAD is the only durable device allowed for use in Japan for Profile-1 patients, the outcome of Profile-1 patients at our institution is acceptable. Furthermore, 12 surviving patients who could not wean from paracorporeal VAD successfully underwent conversion of paracorporeal VAD to implantable CF-LVAD, and they all had favorable course after BTB therapy.

The second important clinical contribution of this study is the detailed description of therapeutic strategies for using paracorporeal VAD in Profile-1 patients. Almost half of the Profile-1 patients required not only LVAD, but also

RVAD, while the majority of patients with BiVAD initially used an RVAD-ECMO system due to complications of critical pulmonary edema. Only one patient was implanted with a durable BiVAD system from the start. This patient received durable BiVAD implantation since the beginning because the patient had been recognized to have severe biventricular failure for several months, and to require biventricular support when the patient undergoes VAD implantation. Pre-operative patient characteristics were compared across therapeutic strategies for VAD, and patients treated with BiVAD-ECMO were in more critical pre-operative condition with more frequent p-ECMO support than those treated with LVAD alone. Since p-ECMO is an effective first-line rescue strategy for patients with cardiogenic shock, in terms of its low invasiveness and promptness in establishing circulatory support, the majority of Profile-1 patients are commonly supported by p-ECMO before VAD implantation [10–13]. Our study cohort included 18 patients who received pre-operative p-ECMO for initial and temporary circulatory support. However, despite its advantages, unnecessary long-term p-ECMO support without native cardiac recovery often results in critical pulmonary injury due to both retrograde blood drainage and perfusion of native circulation systems. [9, 14]. In such cases with critical pulmonary injury due to pulmonary edema, the ECMO circuit is used for RV support as an initial therapeutic strategy. The proper use of p-ECMO in Profile-1 patients, in terms of the support period and appropriate timing to convert to VAD, is still controversial and remains an important question for future research. From the point of view of etiology, patients treated with BiVAD-ECMO mainly had FM ($n = 8$), plus one case of PPCM, which usually develops acutely and involves both left and right ventricles [15, 16]. Insufficient HF medication and a smaller LV and thicker septal wall resulting in part from cardiac edema may reflect etiological differences such as onset patterns between patients with LVAD and BiVAD-ECMO. Furthermore, since planned BiVAD implantation has been recommended because of its likely favorable outcome compared to delayed BiVAD implantation, we are always preparing for BiVAD implantation in patients with acute-onset FM and PPCM [17]. In terms of post-operative outcomes, patients treated with the BiVAD-ECMO strategy required longer operative time, greater transfusion volume, longer ICU stay, longer ventilation time, and more frequent hemodialysis after VAD implantation. However, despite the pre-operative and post-operative critically ill condition with multiple organ failure in patients treated with the BiVAD-ECMO strategy, 8 of 10 such patients had favorable clinical outcomes, comparable to those of LVAD. We consider that this strategy, despite being technically complicated with critical pre- and post-operative conditions, is an essential rescue option for Profile-1 patients complicated by both RV failure and severe pulmonary edema.

Study limitations

This study has several limitations. First, it was a retrospective study in a single center with a relatively small sample size. However, our detailed reporting of etiology, device strategy, and clinical course is still important in the clinical practice of this field. Second, the device strategy for VAD differs somewhat from institution to institution. Nevertheless, since device strategies for VAD in Profile-1 patients can provide helpful information to cardiac physicians and surgeons working in this field, we believe that our report could be a meaningful reference with regard to current device strategies.

Conclusion

Profile-1 patients present various etiologies, and almost half of such cases are associated with acute-onset diseases such as FM, AMI, and PPCM. Therefore, VAD implantation for Profile-1 patients is an inevitable clinical issue at this time. Furthermore, because of their diverse etiologies and pre-operative conditions, not only simple LVAD, but also RVAD and RVAD-ECMO were necessary for our initial therapeutic strategies using VAD. With respect to prognosis, only 6 of 23 Profile-1 patients died within 90 days post-operatively. Furthermore, despite such critical pre-operative conditions, the clinical outcomes of Profile-1 patients with BiVAD-ECMO were comparable to those with LVAD alone. In conclusion, the BiVAD-ECMO system is thought to be an effective therapeutic choice for Profile-1 patients with multiple organ failure. Future investigations must continue to refine strategies for using VAD to rescue these high-risk Profile-1 patients.

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Compliance with ethical standards

Conflict of interest None of the authors declare any competing interest.

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