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Improved long-term performance of pulsatile extracorporeal left ventricular assist device

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Summary
Background and purpose: The majority of heart transplant (HTx) candidates require left ventricular assist device (LVAD) support for more than 2 years before transplantation in Japan. However, the only currently available device is the extracorporeal pulsatile LVAD. The long-term management of extracorporeal LVAD support has improved remarkably over the years. To determine which post-operative management factors are related to the long-term survival of patients on such LVAD, we retrospectively compared the incidence of complications and their management strategies between the initial and recent eras of LVAD use, classified by the year of LVAD surgery.

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Methods: Sixty-nine consecutive patients supported by extracorporeal pulsatile LVAD as a bridge to HTx between 1994 and 2007 were reviewed retrospectively. The patients were assigned according to the time of LVAD surgery to either group A (*n* = 30; between 1994 and 2000) or group B (*n* = 39; between 2001 and 2007).

Results: Patients in group B survived significantly longer on LVAD support than those in group A (674.6 vs. 369.3 days; *p* < 0.001). The 1- and 2-year survival rates were significantly higher in group B than that in group A (82% vs. 48%, *p* < 0.0001; 68% vs. 23%, *p* < 0.0001, respectively). The proportion of deaths due to cerebrovascular accidents was lower (17% vs. 50%, *p* < 0.001) in group B compared with group A. The incidences of systemic infection were similar in both groups, but the proportions of patients alive and achieving transplant surgery after systemic infection were higher in group B than those in group A (55% vs. 14%, *p* < 0.01; 14% vs. 36%, *p* < 0.05, respectively).

Conclusions: The long-term survival of patients even on ''first-generation'' extracorporeal LVAD has improved significantly in the recent era. Careful management of cerebrovascular accidents and systemic infection will play important roles in the long-term LVAD management.

Introduction

Heart transplantation provides considerable survival benefits for patients with end-stage heart failure, but it is available for only a small fraction of such patients [1] due to donor shortage [2]. Therefore, most patients on the heart transplant waiting list require long-term support by a left ventricular assist device (LVAD). Only 60 heart transplants have been performed over the past 10 years in Japan. Therefore, the mean waiting period of Japanese transplant candidates after LVAD surgery often exceeds 2 years and occasionally reaches 4 years [3].

However, the ''first-generation'' pulsatile extracorporeal LVAD (Toyobo-LVAS®; Toyobo-National Cardiovascular Center, Osaka, Japan) is the only type of LVAD covered by the National Health Insurance System in Japan, and implantable LVADs have not yet been approved for coverage. Next generation devices such as the HeartMate XVE® (Thoratec Corp., Pleasanton, CA, USA, and Texas Heart Institute, Houston, TX, USA) and Norvacor® (World Heart, Inc., Oakland, CA, USA) have completed clinical trials in Japan and are now undergoing review and approval by the Ministry of Health, Labor and Welfare [4—6]. A new rotary pump device is also under review [7].

Extracorporeal LVAD was primarily designed for short-term support, but it is used in Japan over the long term as a 'bridge-to-transplant' device. Patients supported by pulsatile extracorporeal LVAD cannot be discharged from the hospital, and cannot leave the intensive care ward without attendant medical doctors. Thus, the use of LVAD as a 'destination therapy' has not yet been approved by the Ministry of Health, Labor and Welfare. This means that transplant candidates supported by LVAD in Japan must remain in the intensive care ward for more than 2 years before receiving a transplant, except when undergoing cardiac rehabilitation outside the ward. Since patients supported by extracorporeal LVAD were not eligible for taking a shower or a bath, Higashi et al. [8] applied appendicular thermal therapy to one patient and reported that the therapy was safe, attenuated psychological and physical stress of the patient, and had the potential of improving cardiac function.

As a result of the recent advances in the management techniques for pulsatile extracorporeal LVAS, the survival rate and transplant rate of patients supported by pulsatile extracorporeal LVAS have improved considerably [9]. To accomplish long-term pulsatile extracorporeal LVAD support, detailed observations as well as rapid responses to LVAD-related complications are essential. The REMATCH study [5,10] showed that sepsis is the leading cause of death (29.5%) after LVAD surgery while cerebrovascular accidents (CVA) are the third cause of death (9.0%). The present study focused on CVA and infection as major complications in patients supported by pulsatile extracorporeal LVAD in Japan, and investigated the current responses to such complications. Although only one type of pulsatile extracorporeal VAD (Toyobo-VAS®) is available in Japan, we speculate that the recent management techniques and the responses to pulsatile extracorporeal LVAD-related complications investigated in this study would also be useful for managing other types of LVAD such as the axial flow types [11—14].

Methods

Patients and study design

We retrospectively reviewed 69 consecutive patients at our institution who were supported by pulsatile extracorporeal VAD (Toyobo-VAS®) as a bridge to heart transplantation between April 1994 and March 2007. Patients supported by LVAD as a bridge to recovery and/or rescue therapy for surgical complications, acute myocarditis, or acute onset of extensive coronary artery occlusion were excluded from this study. To investigate how management techniques have changed over time, patients were assigned to two groups according to the time of LVAD surgery. Thirty patients who had LVAD surgery between 1994 and 2000 were assigned to group A, and 39 patients who underwent surgery between 2001 and 2007 were assigned to group B. All patients received warfarin with a target prothrombin time-international normalized ratio (INR) range of 3—4 [15]. All patients received pre- and peri-operative prophylactic antibiotic treatment with vancomycin and aztreonam.

Overall survival after LVAD surgery, eligibility for heart transplant, duration of support, and complications and managements were compared between the two groups. All the patients provided written informed consent with regard to use of the pulsatile extracorporeal device. The present study

Table 1 Demographic and clinical characteristics of patients.

Parameter	Group A (n = 30)	Group B (n = 39)	p-Value
Age at LVAD implantation (y)	35.1 ± 14.7	33.9 ± 10.8	0.697
Male (%)	15(50%)	19(50%)	0.891
Reason for LVAD implantation (no. of patients, %)			
Dilated cardiomyopathy	25 (83.3%)	31 (79.5%)	0.924
Dilated phase hypertrophic cardiomyopathy	3 (10.0%)	3 (7.7%)	0.925
Ischemic cardiomyopathy	1 (0.3%)	2 (5.1%)	0.816
Others	1 (0.3%)	3 (7.7%)	0.804
Treatment at time of LVAD surgery (no. of patients, %)			
Ventilator	12 (40.0%)	15 (38.4%)	0.901
IABP	8 (26.7%)	10 (25.6%)	0.857
PCPS	2 (6.6%)	3 (7.7%)	0.760
Continuous intravenous inotropic agents	30(100%)	39(100%)	—
Warfarin	9 (30.0%)	12 (30.8%)	0.845
Aspirin	13 (43.3%)	15 (38.5%)	0.871
Diuretic	30(100%)	39(100%)	—
β-Blockers	6 (20.0%)	8 (42.1%)	0.803
ACE inhibitors or A-II antagonists	12 (40.0%)	14 (35.9%)	0.922
Hemodynamic variables within 5 days from LVAD surgery			
CI (L min^{-1} m^{-2})	2.1 ± 0.5	2.1 ± 0.4	0.852
PAWP (mmHg)	25.0 ± 8.9	27.9 ± 10.6	0.345
Mean PA (mmHg)	29.7 ± 10.6	32.6 ± 9.6	0.367
Mean RA (mmHg)	11.3 ± 6.3	10.7 ± 6.8	0.764
Laboratory data within 5 days from LVAD surgery			
TP (g/dL)	6.5 ± 0.2	6.3 ± 0.2	0.422
T-Bil (mg/dL)	2.9 ± 0.4	2.0 ± 0.4	0.111
BUN (mg/dL)	26.9 ± 4.0	38.7 ± 3.67	0.034
Cre (mg/dL)	1.2 ± 0.2	1.8 ± 0.2	0.016
BNP (pg/mL)	738.7 ± 197.6	1436.5 ± 178.8	0.011
Inflow cannula drainage site			
Left atrium drainage	14 (46.7%)	1(2.6%)	<0.0001
Left ventricular drainage	16 (53.3%)	38 (97.4%)	<0.0001

LVAD, left ventricular assist device; IABP, intra aortic balloon pumping; PCPS, percutaneous cardiopulmonary support; ACE, angiotensin-converting enzyme; A-II, angiotensin II; CI, cardiac index; PAWP, pulmonary arterial wedge pressure; PA, pulmonary artery pressure; RA, right atrial pressure; TP, total protein; T-Bil, total bilirubin; BUN, blood urea nitrogen; Cre, creatinine; BNP, brain natriuretic peptide.

was approved by the Institutional Review Board and the Institutional Ethical Committee for Human Research at the National Cardiovascular Center, and conducted according to the Declaration of Helsinki.

Statistical analysis

Data are presented as means ± SD. Normality was evaluated for each variable on the basis of normal distribution plots and histograms and by the Kolmogorov—Smirnov test. Clinical characteristics, duration and outcome after LVAD surgery, and complications were compared between groups using Student's unpaired two-tailed *t*-test or chi-square analysis. Survival after LVAD surgery was compared using the Kaplan—Meier analysis and log rank statistics. All statistical analyses were performed using the JMP 7.0 software (SAS Institute, Cary, NC, USA).

Results

Support duration and prognosis

Table 1 summarizes the demographic and clinical data in groups A and B. Age and gender distribution did not differ between groups A and B. The profiles of mechanical support and/or drug administration at the time of LVAD surgery also did not differ significantly between the two groups. Hemodynamic variables obtained by pulmonary artery catheterization within 5 days prior to LVAD surgery or at the time of operation were not significantly different between the groups. Nutritive status as reflected by total serum protein was not different, either. Although liver function as indicated by total bilirubin was not significantly different, the indexes of renal function such as serum urea nitrogen and creatinine level were significantly elevated in group B compared with group A. Serum concentration of

Table 2 Outcome after left ventricular assist device surgery.

Parameter	Group A (n = 30)	Group B (n = 39)	p-Value
Duration of LVAD support (days)	369.3 ± 337.2	674.6 ± 321.3	0.0003
Outcome (no. of patients, %)			
Transplanted in Japan	6 (20.0%)	11 (28.2%)	0.615
Transferred and transplanted outside Japan[a]	2 (6.6%)	4 (10.2%)	0.925
Died	22 (73.3%)	14 (35.9%)	0.005
Remaining on waiting list	0(0%)	10 (25.6%)	0.007

[a] A number of transplant candidates were transferred and underwent heart transplantation outside Japan, due to extreme donor shortage and legal constraints in Japan. Japanese organ transplant law did not have criteria for the diagnosis of brain death for those aged under 15 years, thus, pediatric patients had no chance of receiving heart transplant surgery in Japan.
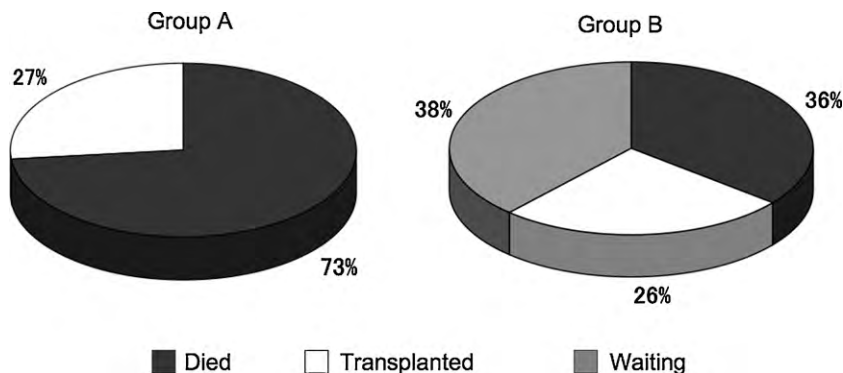

Figure 1 Outcome of transplant candidates after left ventricular assist device surgery in group A (left panel) and group B (right panel).

brain natriuretic peptide (BNP) was higher in group B than that in group A. The site of inflow cannula drainage was distinctly different between groups A and B. Fourteen patients (46.7%) underwent LVAD implantation with left atrium inflow cannula drainage in group A compared with only one patient (2.6%) in group B.

Table 2 and Fig. 1 summarize the outcomes of patients in groups A and B. The duration of LVAD support was significantly longer in group B than that in group A. Mortality was

Figure 2 Kaplan—Meier's survival curves of patients supported by extracorporeal pulsatile left ventricular assist device (LVAD). Survival rates of groups A and B at 100 days, 1 and 2 years after LVAD surgery. Solid line and closed squares, group A; dotted line and open squares, group B.

significantly higher in group A than in group B, and none of the patients in group A were still on the waiting list. Fig. 2 shows the Kaplan—Meier survival curves of the two groups. Survival after LVAD surgery was significantly lower in group A than in group B. The survival rate after LVAD surgery in group B was satisfactory compared to that reported for the post-REMATCH era [8,16,17], although our patients were supported by LVAD as a bridge to transplant, and not as a destination therapy.

Fig. 3 shows the causes of death in groups A and B. The proportion of deaths due to CVA was significantly higher in group A than in group B (50% vs. 13%, $p < 0.0001$), whereas that of infection did not differ significantly between the two groups. The proportion of deaths due to right ventricular failure, defined as fatal liver or renal insufficiency under LVAD support and requirement of inotropic agents, was higher in group B (Fig. 3).
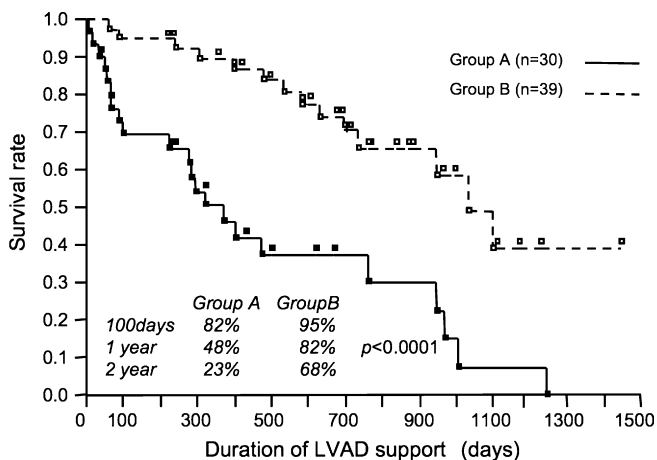
CVA after pulsatile extracorporeal LVAD

Among the 69 patients studied, 37 patients developed CVA after pulsatile extracorporeal LVAD. In this study, CVA was used as a collective term, comprising intracranial hemorrhage and intracranial infarction. The incidence and outcome after CVA in the patients are summarized in Table 3. Rapid reversal of warfarin-induced anticoagulation was attempted in all patients who developed intracerebral hemorrhage [15]. Vitamin K was never used in either group of patients. Prothrombin complex concentrate (PCC), which contains a high level of vitamin K-dependent coagulation
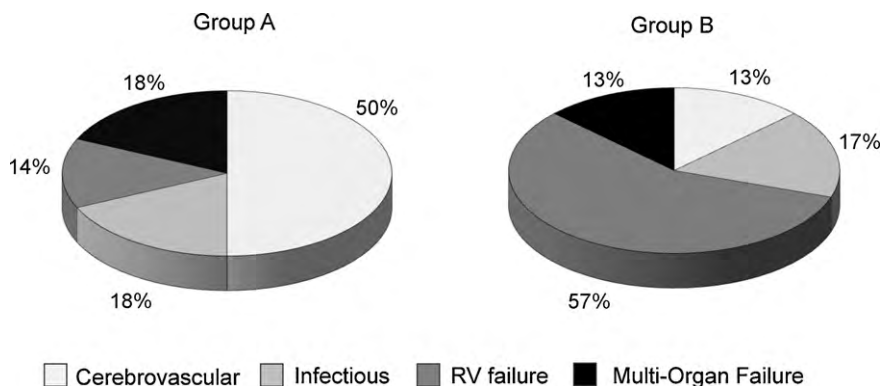
Figure 3 Causes of death in group A (left panel) and group B (right panel). RV, right ventricular.

Table 3 Incidence of cerebrovascular accidents.

Parameter	Group A ($n = 30$)	Group B ($n = 39$)	p-Value
Incidence of CVA (no. of patients, %)	17 (56.7%)	20 (51.2%)	0.841
Intracranial hemorrhage (no. of patients, %)	16 (53.3%)	18 (46.1%)	0.727
Intracranial infarction (no. of patients, %)	13 (43.3%)	12 (30.7%)	0.410
Anticoagulant status			
Baseline INR at stable situation	3.2 ± 1.5	3.3 ± 1.2	0.759
INR on the day of CVA event	3.8 ± 2.1	3.2 ± 1.3	0.149
Among patients developed CVA			
Proportion of CVA requiring neurosurgery (no. of patients, %)	12/17(70.6%)	8/20 (40.0%)	0.062
Proportion of CVA leading to death (no. of patients, %)	11/17(64.7%)	3/20 (15.0%)	0.006
Proportion of patients given PCC (no. of patients, %)	3/17 (17.6%)	12/20 (60.0%)	0.023

CVA, cerebrovascular accident; INR, international normalized ratio; PCC, prothrombin complex concentrate.

factors II, VII, IX and X, rapidly and effectively reverses warfarin-induced anticoagulation [15,18—20]. This product (PPSB-HT®; Nihon Pharmaceuticals, Tokyo, Japan) has been available since 2001, and it has been used at our institution for emergency reversal of warfarin-induced anticoagulation in cases of intracranial bleeding, intraabdominal hemorrhage, and cardiac tamponade [15].

The majority of patients in both groups who developed CVA had a combination of intracranial hemorrhage and intracranial infarction as shown in Table 3, and the frequencies of infarction and hemorrhage were not significantly different between the two groups.

Neither the incidence of CVA nor the proportion of CVA which required subsequent neurosurgery differed significantly between the two groups. However, the proportion of patients in which CVA led to death was significantly higher in group A than in group B. Fig. 4 shows the Kaplan—Meier survival curves of patients who developed CVA in both groups. The survival rates of patients with CVA episodes were significantly lower in group A than in group B.

The proportion of patients treated with PCC after CVA was significantly higher in group B than in group A. To investigate the effect of PCC on the prognosis of patients who developed CVA, the Kaplan—Meier survival curves of patients who developed CVA and treated with or without administration of PCC are shown in Fig. 5. Survival rates tended to be better among patients treated with PCC than those who were not treated with PCC, but the benefit of PCC for survival outcome was not statistically proven.
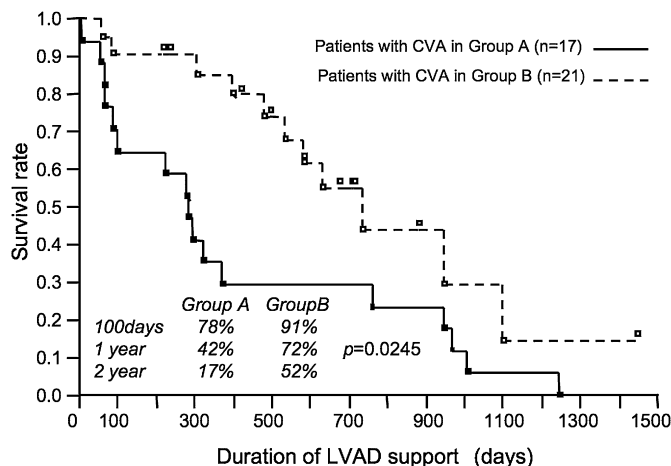

Figure 4 Subgroup analysis of the Kaplan—Meier survival curves of patients who developed cerebrovascular accident (CVA) (group A, $n = 17$ vs. group B, $n = 21$) after extracorporeal pulsatile left ventricular assist device (LVAD) surgery. Survival rates at 100 days, 1 and 2 years after LVAD surgery, of patients in groups A and B who developed CVA. Solid line and closed squares, patients in group A; dotted line and open squares, patients in group B.

Infection after pulsatile extracorporeal LVAD

Among the 69 patients studied, 53 patients developed systemic infection (SI) after pulsatile extracorporeal LVAD. SI

Table 4 Incidence of systemic infection (SI).

Parameter	Group A (n = 30)	Group B (n = 39)	p-Value
Incidence of SI (no. of patients, %)	22 (73.3%)	31 (79.5%)	0.754
Among patients who developed SI			
Proportion of SI leading to death (no. of patients, %)	4/22 (18.2%)	5/31 (16.1%)	0.861
Proportion of patients presently alive (no. of patients, %)	3/22 (13.6%)	17/31 (54.8%)	0.006
Proportion of patients undergoing transplants (no. of patients, %)	3/22 (13.6%)	11/31 (35.5%)	0.049
Cumulative number of SI episodes (cumulative no. of episodes)	76	102	-
Number of episodes per year per patient	1.2 ± 0.3	1.3 ± 0.2	0.240

SI, systemic infection defined as positive blood culture when patients developed any symptoms of infection.
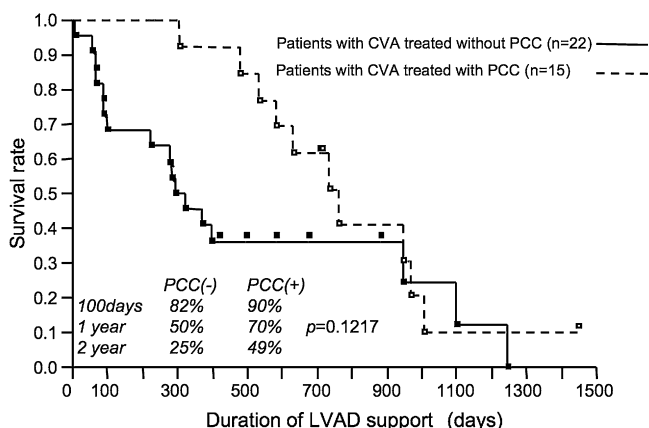

Figure 5 Subgroup analysis of the Kaplan—Meier survival curves of patients who developed cerebrovascular accident (CVA) after extracorporeal pulsatile left ventricular assist device (LVAD) surgery and were treated with prothrombin complex concentrate (PCC) (n = 22) or not treated with PCC (n = 15). Survival rates at 100 days, 1 and 2 years after LVAD surgery, of PCC-treated and non-PCC-treated patients. Solid line and closed squares, patients not treated with PCC; dotted line and open squares, patients treated with PCC.

was defined as a positive blood culture when patients developed any symptom of infection. Table 4 summarizes the incidence of SI among the patients studied. Neither the incidence of patients who developed SI nor the proportion of SI leading to death differed significantly between the two groups. In addition, the cumulative number of SI episodes and the number of SI episodes per year per patient were not significantly different between the two groups. However, although SI itself was not a direct cause of death, a subgroup analysis of patients with a history of SI revealed that the proportion of patients who were alive, including those who received transplant and those who remained on LVAD support, was significantly lower in group A than in group B. The proportion of patients with a history of SI who could undergo transplantation was significantly lower in group A than in group B. The duration from infection to death in patients with a history of SI after LVAD surgery was significantly shorter in group A than in group B (256.0 ± 203.1 vs. 749.7 ± 328.8 days, $p < 0.01$).

Table 5 shows the strains isolated from blood cultures in groups A and B. The proportion of methicillin-susceptible

Staphylococcus aureus (MSSA) was significantly higher in group B than in group A. However, the proportion of other organisms including methicillin-resistant *Staphylococcus aureus* (MRSA) did not differ significantly between two groups. Linezolid is a powerful synthetic oxazolidinone antibiotic against Gram-positive pathogens that produce toxins [21]. It is commonly used to combat severe infection with staphylococci including MRSA. Linezolid has been available at our institution since 2001, and has been administered to patients with recurrent refractory MRSA or MSSA infection under all treatment modalities. To date, 7 of our patients were treated with linezolid, comprising 2 patients in group A and 5 patients in group B. All of the 7 patients treated with linezolid had more than 3 episodes of MRSA or MSSA infection with blood culture positive, in spite of intense antibiotic treatment. Then, we decide to use linezolid under diagnosis of refractory staphylococcal infection. To investigate the effect of linezolid on the prognosis of patients who developed SI with recurrent MRSA or MSSA infection, the survival rates of patients treated with and without linezolid were compared (Fig. 6). A total of 25 patients had refractory SI with MRSA or MSSA. Among them, the survival rate of patients who were treated with linezolid tended to be better than those treated without linezolid, but the difference did not reach statistical significance.

Table 5 Strains isolated from blood cultures.

Strain	Group A (n = 30)	Group B (n = 39)
MSSA[*]	2%	17%
MRSA	20%	25%
Staphylococcus epidermidis	15%	8%
Streptococcus viridans	2%	0%
Staphylococcus capitis	11%	2%
Streptococcus agalactiae	2%	0%
Staphylococcus lugdunensis	7%	6%
Enterobacter aerogenes	2%	0%
Pseudomonas aeruginosa	6%	3%
*Stenotrophomonas maltophili*a	0%	1%
Others	33%	42%

MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-sensitive *Staphylococcus aureus*.
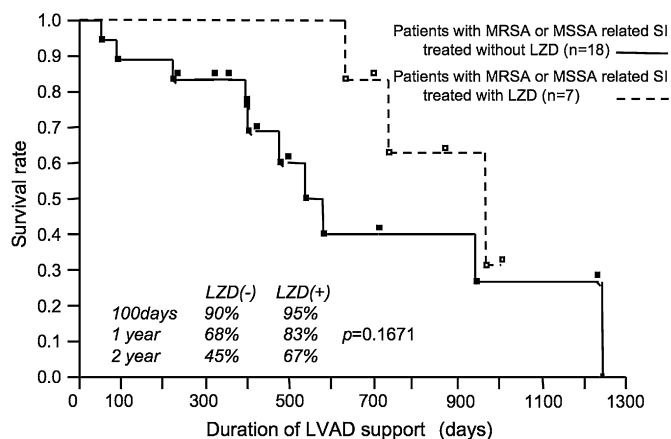[*] $p < 0.0001$.

Figure 6 Subgroup analysis of the Kaplan—Meier survival curves of patients who developed systemic infection (SI) with methicillin-resistant *Staphylococcus aureus* (MRSA) or methicillin-sensitive *Staphylococcus aureus* (MSSA) after extracorporeal pulsatile left ventricular assist device (LVAD) surgery, and who were treated with linezolid (LZD) (*n* = 7) or not treated with linezolid (*n* = 18). Survival rates at 100 days, 1 and 2 years after LVAD surgery, of linezolid-treated and non-linezolid-treated patients. Solid line and closed squares, patients not treated with linezolid; dotted line and open squares, patients treated with linezolid.

Discussion

We found that even the first generational extracorporeal LVAD can achieve sufficient long-term support. Extracorporeal LVAD has been withdrawn as the first-line mechanical circulatory support worldwide, and its use is limited to short-term support or for pediatric patients [22—24]. However, it is currently the only device that is officially approved in Japan by the National Health Insurance System, therefore patients with severe heart failure who need LVAD as a bridge to transplant have no other choice at present.

Several studies have investigated the feasibility of long-term LVAD usage, but all of them examined implantable devices [9,16,17,25]. To the best of our knowledge, this is the first study to investigate the outcomes of long-term support with pulsatile extracorporeal LVAD and the complications in using such type of LVAD. We found that pulsatile extracorporeal LVAD can support patients for an average of 660 days (including patients with ongoing support). This finding is equal or superior to that reported in the post-REMATCH era, even considering the difference in the proportion of patients.

The present study found that survival outcome has improved dramatically over the past 8 years even though the probability of complications did not differ. The improvement might be associated with progress in careful and prompt management for complications. The important impediments to long-term LVAD support are CVA, infections, and right heart failure [11,26,27]. Although the incidence of CVA did not differ significantly, the number of patients who died of CVA has recently become appreciably lower. The incidence of SI has not changed, but the management of patients who become systemically infected has improved significantly. In the present study, we speculated that these improve-

ments might be associated with prompt administration of PCC for CVA and well-selected administration of linezolid for staphylococcus-related SI.

We used the term CVA collectively for both cerebral hemorrhage and cerebral infarction. The prognosis is generally expected to be worse for cerebral hemorrhage than cerebral infarction, and PCC was used only in patients with hemorrhage in this study. However, most patients developed cerebral hemorrhage after infarction, and 90% or more of the patients with CVA in both groups had cerebral hemorrhage (Table 3). Therefore, we analyzed cerebral hemorrhage and infarction together under the broad term CVA. Nevertheless, this might have limited to some extent the analysis of the effectiveness of PCC in managing patients with CVA. In the present study, the use of PCC did not significantly improve the prognosis of patients with CVA (Fig. 5); however, other studies [15,19,28,29] have shown that PCC is effective against intracranial hemorrhage. Indeed, we recently reported that the proportion of patients' survival on LVAD after intracranial hemorrhage events was significantly increased when treated with PCC compared to that when treated without PCC administration [15]. Huttner et al. [28] have shown that the incidence of hematoma growth is significantly lower in patients with warfarin-associated intracranial hemorrhage who received PCC than in those who did not. Further studies are needed to evaluate the efficacy of PCC to prevent fatal intracranial hematoma growth in patients supported by LVAD who developed CVA.

Although a high frequency of side effects has limited its use, linezolid is reported to be superior to vancomycin for treating MRSA infection [30,31]. In addition, linezolid is a powerful drug to treat severe infections by not only MRSA, but also other Gram-positive bacteria, even in peculiar anatomical sites in which therapeutic levels of antibiotics cannot be achieved [32]. Falagas et al. [33] reviewed the literature and reported the effectiveness of linezolid for endocarditis due to multidrug-resistant Gram-positive cocci. Coagulase negative staphylococci and *Staphylococcus aureus* have been reported to be the most common pathogens in LVAD-related infections [34]. Indeed, as shown in Table 5, most of our patients who had SI were infected by Gram-positive pathogens. Therefore, linezolid might be a useful antibiotic agent for treating the most common responsible pathogens in LVAD patients.

We failed to demonstrate statistically the contribution of linezolid in improving the survival of patients with LVAD-related MRSA or MSSA infectious, and the number of the patients treated with linezolid in this study was too small to prove the effectiveness of linezolid. However, all patients with MRSA or MSSA related SI who were treated with linezolid could survive more than 600 days on LVAD, whereas those not treated with linezolid tended to show poorer survival (Fig. 6). Although we do not have an institutional protocol of linezolid administration, we used linezolid only in patients with refractory staphylococcal infection, and the conditions of patients treated with linezolid are assumed to be severer than those not treated with linezolid. Further prospective studies are needed to validate the superiority of linezolid use over existing antibiotic regimens, and to establish the appropriate dosage and regimen of this drug for these patients. Although not observed in this study, linezolid-resistant *Staphylococcus* is becoming

a recent concern in severe SI [35], which requires careful observation.

One of the limitations of this study was that we did not identify the causes of infections, which vary depending on the duration after LVAD implantation. In the acute phase, infectious complications may be related to preoperative condition, and/or surgical intervention. In the chronic phase, they are mostly due to infection of exit sites of inflow and/or outflow cannulae. Driveline infections may require surgical debridement [36]. LVAD-associated endocarditis and bacteremia may relapse after prolonged courses of antibiotics [37]. Although heart transplantation could cure LVAD-related endocarditis by removal of the infected heart [38,39], the mean waiting period of Japanese transplant candidates exceeds 2 years. Therefore, since we need to treat infections chronically regardless of the causes, we did not analyze the causes of infection in this observation.

The major limitation of this study was that the inflow cannula drainage site had been changed from the left atrium to the left ventricle over the years, and most of the patients nowadays undergo LVAD surgery with inflow cannula drainage at the left ventricle. The biggest difference between these two systems may be the bypass flow ratio, and this difference possibly impacts the survival rate. However, we were not able to pursue the bypass flow ratio of patients supported by LVAD with left atrial blood drainage. A difference in flow ratio between groups A and B could possibly influence the analysis of survival. In addition to the difference of flow ratio and a higher tendency of clot formation in LVAD with left atrial cannula than that with left ventricular cannula, Sakamoto [40] reported that LVAD with ventricular cannula maintained normal cellular anatomy and reserve inotropic power during support, and patients were exposed to less elevated afterload compared to LVAD with atrial cannula. These advantages of ventricular cannula to atrial cannula could also be a factor contributing to better outcome in group B than in group A, despite the less favorable preoperative conditions in group B as reflected by more deteriorated renal insufficiency and higher BNP level in this group.

Clinical implications

Although extracorporeal LVAD is no longer a first-line mechanical support device in many countries, the main complications are the same as those of new generation devices. LVAD drainage site could be one of the most important factors contributing to the long-term survival of patients on LVAD, which affect the incidence of infection, clot formation, or other complications. However, we did want to focus on the recent progression in management of LVAD-related complication in the present manuscript. Our skill in device management has improved because patients who await transplants for a mean of over 2 years require intensive care. In addition, the number of patients who require LVAD as a 'destination therapy' is increasing worldwide. Therefore, the importance of the device itself and the management skills for long-term use is increasing. In that sense, the present findings derived from our observations should help patients supported by LVAD even with a new generation device, to be carefully treated in the face of an increasing incidence of chronic complications such as infection or CVA.

Study limitations

This is single-center, retrospective analysis of patients supported by a single device. All patients were on the device as a bridge-to-transplant strategy, therefore the baseline characteristics differ from those of other reported investigations on the feasibility of long-term support. The patient cohort was relatively small, and some of our results might be quite different in a larger population.

Conclusion

In conclusion, we showed that the long-term survival of patients on pulsatile extracorporeal LVAD has improved recently due to delicate and timely treatment of LVAD-related complications. The management of CVA and SI play an important role in long-term LVAD support.

Conflict of interest

This study did not receive financial support and the authors declare no conflicts of interest.

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