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ORIGINAL ARTICLE

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Fifteen-year experience with Toyobo paracorporeal left ventricular assist system

Abstract Our 15-year experience of the Toyobo paracorporeal left ventricular assist system (LVAS) at Osaka University Hospital was reviewed. In total, 61 patients underwent Toyobo LVAS implantation from January 1992 to August 2007. Their mean age was 38.1 ± 16.9 years. The etiologies of heart failure were idiopathic dilated cardiomyopathy in 35 patients, ischemic cardiomyopathy in 15, myocarditis in 5, secondary cardiomyopathy in 4, and others in 2. Preoperatively, intubation was required in 41 patients (67.3%), an intra-aortic balloon pump was required in 38 (62.3%), and extracorporeal membrane oxygenation was required in 30 (49.2%). Four patients underwent heart transplantation and 11 underwent LVAS removal. Of those 11 patients, 4 were subjected to emergent removal because of device complications and all of them died. Of the 7 patients that underwent scheduled LVAS removal, heart failure recurred in 2 patients and reimplantation was required. In terms of major device-related complications, cerebral hemorrhage occurred in 16 patients (26.2%), cerebral infarction in 19 (31.1%), mediastinitis in 10 (16.4%), and inflow/outflow cannula exit site infection in 19 patients (31.1%). The actuarial survival rate of the patients operated on in the last 5 years of this study was 66.3% at 6 months and 45.9% at 1 year. Although the survival rate of patients supported by the Toyobo LVAS has recently improved, the morbidity rate is significant. Considering the current severe shortage of heart donors in Japan, it is important to introduce more durable devices with fewer complications and to establish the strategies for using the LVAS as a bridge to recovery.

Key words Toyobo left ventricular assist system · Paracorporeal · Bridge to transplantation · Bridge to recovery

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Introduction

The Toyobo left ventricular assist system (LVAS; Nipro, Tokyo, Japan) is a paracorporeal, pneumatic, diaphragm-type LVAS. The pumps are made of Toyobo TM-series segmented polyether polyurethane without a seam. The effective stroke volume is 70 ml and the maximum output in a mock system is 7.0 l/min.[1–3] The first clinical application of this device took place in 1982 at the National Cardiovascular Center for a patient with postcardiotomy shock;[4] the device became commercially available in 1990. At first, this device was used only for acute heart failure in patients with postcardiotomy cardiogenic shock.[5,6] In 1992, we experienced the first patient with dilated cardiomyopathy who was transported from Japan to the United States by air and was successfully bridged to transplantation after 119 days of support.[7] Since then, its use for chronic heart failure due to cardiomyopathy has gradually increased.[8] Since the left ventricular apical drainage system became available in 1999, the left ventricular apex has been the first choice for the inflow site. After the first heart transplantation in Japan in 1999, the Toyobo LVAS has been the main device available for bridge to transplantation. We review our experiences with the Toyobo LVAS and analyze the factors related to its results.

Materials and methods

From January 1992 to August 2007, 61 patients underwent a total of 65 Toyobo LVAS implantations at Osaka University Hospital. Forty-eight of these patients were male. The age of the patients ranged from 7 to 69 years, with a mean of 38.1 ± 16.9 years. The indication for LVAS implantation was irreversible end-stage heart failure with NYHA class IV symptoms and imminent or already present end-organ dysfunction despite optimal medical therapy including inotropic agents. Since 1994, implantable LVASs such as the HeartMate (Thoratec, Pleasanton, CA, USA) and the Novacor (WorldHeart, Oakland, CA, USA) have become

Table 1. Preoperative and operative characteristics ($n = 61$)

Male (%)	78.7
Mean age (years)	38.1 ± 16.9 (range 7–69)
Mean body surface area (m^2)	1.56 ± 0.25 (range 0.80–1.98)
Diagnosis (no. of patients)	
Idiopathic cardiomyopathy	35
Ischemic cardiomyopathy	15
Myocarditis	5
Secondary cardiomyopathy	4
Others	2
Preoperative status (no. of patients)	
Catecholamine	61
Mechanical ventilation	41
Intra-aortic balloon pump	38
Extracorporeal membrane oxygenation	30
Blood examinations	
BUN (mg/dl)	38.8 ± 26.5
Creatinine (mg/dl)	1.7 ± 1.2
AST (IU/l)	353 ± 972
ALT (IU/l)	453 ± 1057
Total bilirubin (mg/dl)	5.9 ± 7.5
Total protein (mg/dl)	6.2 ± 1.3
White blood cells ($\times 10^3/\mu l$)	11.4 ± 6.4
CRP (mg/dl)	10.2 ± 9.9
Brain natriuretic peptide (pg/ml)	1632 ± 1311
Echocardiography data	
LVDd (mm)	63.6 ± 12.4
LVDs (mm)	57.3 ± 12.6
Ejection fraction (%)	21.4 ± 12.6
Mitral regurgitation >II (no. of Patients)	27
Right heart catheterization	
Heart rate (bpm)	107 ± 22
Systolic blood pressure (mmHg)	92 ± 18
Systolic pulmonary artery pressure (mmHg)	48 ± 15
Pulmonary capillary wedge pressure (mmHg)	23 ± 10
Cardiac index ($l/min/m^2$)	1.9 ± 0.6
Concomitant procedures (no. of patients)	
Mitral valve repair	21
Tricuspid annuloplasty	17
Left ventricular restoration	4
Aortic valve replacement	2
Coronary artery bypass grafting	2
Biventricular lead implantation	2

BUN, blood urea nitrogen; AST, aspartate aminotransferase; ALT, aranin aminotransferase; CRP, C-reactive protein; LVDd, left ventricular diameter at end diastole; LVDs, left ventricular diameter at end systole

available for use in our institution, but these devices were used only in a limited number of patients with sufficient body size (body surface area >1.50 m^2) who had been registered as heart transplantation candidates. As a result, the Toyobo LVAS was selected for patients with a smaller body size, those with significant preexisting complications who could not be registered as transplantation candidates, or those with acute deterioration of heart function.

The patients' preoperative status is summarized in Table 1. The body surface area was less than 1.50 m^2 in 20 patients (32.3%). Idiopathic cardiomyopathy was the leading cause of heart failure, especially in the younger patients (72.7% of patients <21 years old). Ischemic cardiomyopathy was the second leading cause and the percentage increased with age (47.1% of patients >50 years old) (Fig. 1). All patients had NYHA class IV heart failure symptoms and were dependent on inotropic support. More than half of the patients required mechanical ventilation and mechanical circulatory support preoperatively. Eighteen patients

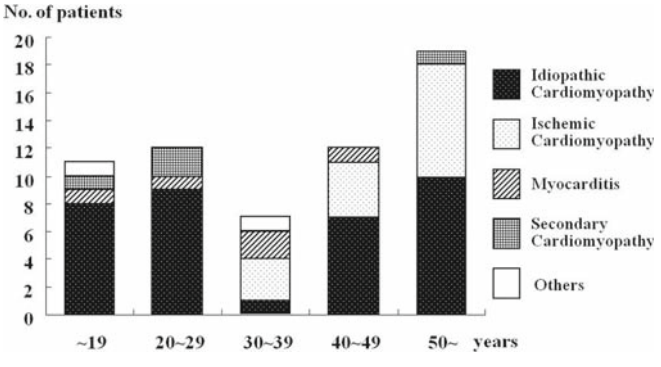

Fig. 1. Age-specific etiology of heart failure. Idiopathic cardiomyopathy was the leading cause, especially in the younger patients, and the number of patients with ischemic cardiomyopathy increased with age

(29.5%) had renal dysfunction (serum creatinine level ≥2.0 mg/dl) and 20 patients (32.8%) had liver dysfunction (serum total bilirubin level ≥5.0 mg/dl).

All the implantation procedures were performed through median sternotomy and under standard cardiopulmonary bypass. We prefer to perform all the procedures without cardioplegic cardiac arrest unless the left ventricle is seriously damaged by acute myocardial infarction or left ventricular thrombus is identified. To facilitate future LVAS explantation, concomitant procedures, including left ventricular restoration, mitral valve repair, tricuspid annuloplasty, and biventricular lead implantation, were performed as described in Table 1. If LVAS filling was poor at weaning from cardiopulmonary bypass even with adequate right atrial pressure and support for the right ventricle using nitric oxide (NO) inhalation and catecholamine, a right ventricular assist system (RVAS) using an extracorporeal membrane oxygenation (ECMO) system (RVAS-ECMO) was established. If right heart failure was so severe that the surgeons considered weaning from the RVAS-ECMO impossible within 1 week, RVAS using a Toyobo pump was established instead of ECMO.

In the first 24 h after the operation, the patients received no anticoagulation therapy. Thereafter, if there was no significant drainage from the chest tube, continuous heparin infusion was started and activated partial thromboplastin time was maintained at 150%–200% of the normal value. Long-term anticoagulation medication consisted of warfarin (dosage according to international normalized ratio 3–3.5) and aspirin 100 mg/day. Ticlopidine 200 mg/day has also been added since October 2003. Medical treatments for heart failure were started as soon as the patient's general condition had stabilized. The current regimen includes angiotensin-converting enzyme inhibitors, spironolactone, and a β-blocker (carvedilol). Carvedilol is initiated at a dosage of 2.5 mg/day and is doubled every week until a dosage of 20–40 mg/day is reached. The heart function was evaluated by echocardiography every week in the first month and every month thereafter, as long as there was a possibility of recovery. Serum brain natriuretic peptide level was monitored every month. The LVAS pump head was exchanged when fresh red or floating thrombi that were likely to detach from the pump wall were observed, or when the presence of infected thrombi was suspected.

The hospital records of the 61 patients were retrospectively reviewed. Preoperative status, operative strategies, and clinical outcomes were evaluated. This study was approved by the ethical committees of Osaka University Graduate School of Medicine. All patients provided their written informed consent.

Results

After LVAS implantation, patients showed significant improvements in hemodynamics and organ function (Fig. 2). The mean duration of LVAS support was 224 ± 283 days. Five patients underwent heart transplantation at 21, 119, 265, 853, and 954 days after LVAS implantation (two abroad and three at Osaka University Hospital). Eleven patients underwent LVAS removal. Of these 11 patients, 4 underwent emergent LVAS removal because of complications such as infection or cerebral hemorrhage. Two of them died of sepsis after LVAS removal and two of them died of multiple organ failure and cerebral hemorrhage after reimplantation of a LVAS. Of the seven patients for whom the LVAS was removed as scheduled, heart failure recurred in two patients and they underwent reimplantation of the Toyobo LVAS. The longest duration of LVAS support was 2000 days and is still ongoing. The overall actuarial survival rate was 52.2% at 6 months and 36.3% at 1 year. The survival rate has improved recently, and the actuarial survival rate of the patients operated on in the last 5 years of this study was 66.3% at 6 months and 45.9% at 1 year. This was significantly better than the survival rates attained before 2003 (Fig. 3A).

Table 2. Postoperative complications ($n = 61$)

Complication	No. of patients (%)
Right heart failure	
Required RVAS during the operation	20 (32.8)
RVAS-ECMO	17
Toyobo-RVAS	3
Required RVAS postoperatively	3 (4.9)
Reoperation for bleeding/cardiac tamponade	18 (29.5)
Cerebrovascular events	
Cerebral infarction	19 (31.1)
Cerebral bleeding	16 (26.2)
Thrombus formation in the pump (required pump-head exchange)	29 (47.5)
Device-related infection	
Positive blood culture	36 (59.0)
Inflow/outflow cannula exit site infection	19 (26.2)
Mediastinitis	10 (16.4)
Respiratory failure (tracheostomy)	20 (32.8)
Renal failure (temporary hemodialysis)	25 (41.0)

RVAS, right ventricular assist system; ECMO, extracorporeal membrane oxygenation

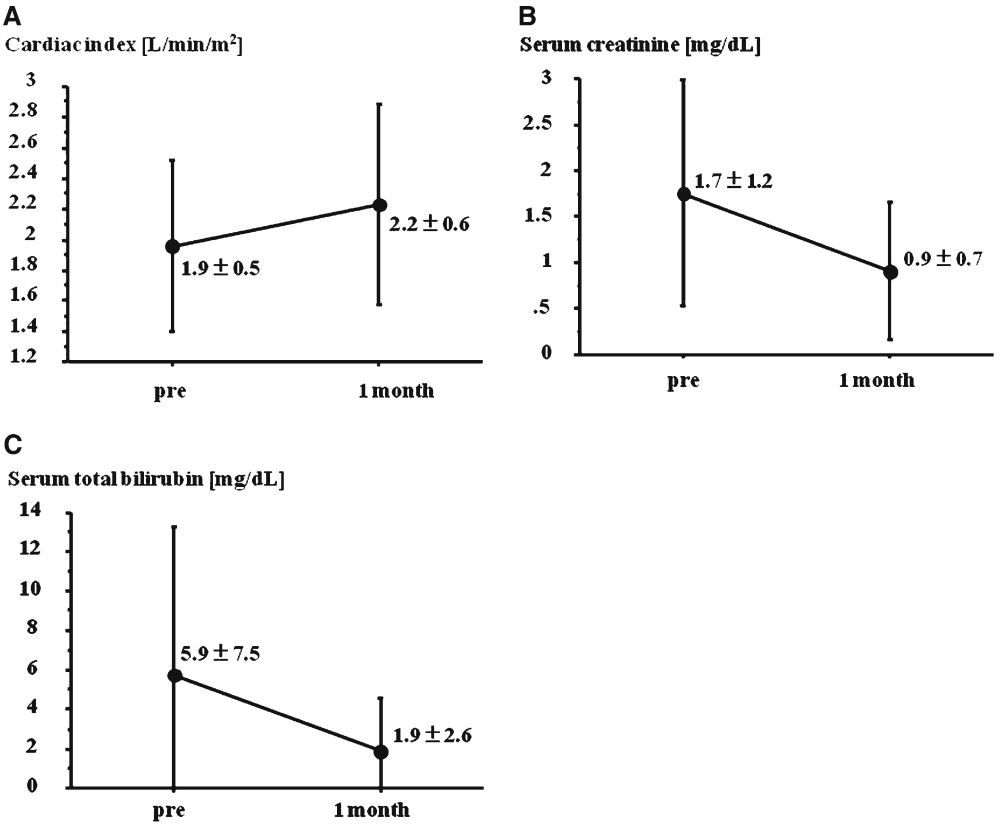

Fig. 2. Changes in cardiac index, serum creatinine, and serum total bilirubin level after left ventricular assist system (LVAS) implantation (at 1 month after the operation). **A** Cardiac index increased from 1.9 ± 0.5 to 2.2 ± 0.6 l/min/m^2, **B** serum creatinine level decreased from 1.7 ± 1.2 to 0.9 ± 0.7 mg/dl and **C** serum total bilirubin level decreased from 5.9 ± 7.5 to 1.9 ± 2.6 mg/dl

The postoperative complications are summarized in Table 2. RVAS-ECMO was required in 17 patients (27.9%). Of these 17 patients, RVAS-ECMO was removed in 8 and was converted to Toyobo RVAS in 2 patients. The other 7 patients died while under support by RVAS-ECMO. Three patients underwent Toyobo RVAS implantation from the beginning. Toyobo RVAS was also required in three patients after LVAS implantation due to persistent right heart failure. No patient under Toyobo RVAS support survived to transplantation or recovery. The mean duration of biventricular support with the Toyobo pump was 136 ± 114 days (range 19–353 days). Among the preoperative and operative parameters, multivariate analysis using the Cox hazard model revealed that the preoperative requirement of ECMO and the preoperative serum creatinine level were independent risk factors for requiring mechanical right heart support (Table 3). Reoperation for bleeding and/or late cardiac tamponade was required in 18 patients (29.5%). The most common and significant complications were cerebrovascular events. The cerebrovascular event-free curve is shown in Fig. 3B. Most cerebrovascular events occurred in the first 6 months after the implantation, and the frequency decreased after 1 year. The cerebrovascular event-free rate did not improve significantly for operations performed after 2002 (P = 0.0686, log rank test). Cerebral hemorrhage was observed in 16 patients (26.2%) and cerebral infarction in 19 patients (31.1%). Among preoperative and operative parameters, early-period operation (before 2003) and left atrial drainage were the significant risk factors for cerebrovascular events as determined by univariate analysis using the Cox hazard model. However, neither of these factors was identified as an independent risk factor by multivariate analysis (Table 4).

Thrombus formation in the pump was observed in the majority of patients under long-term support. Exchange of the LVAS pump head was required in 62% of the patients under support for more than 30 days. The number of exchanges in patients under support for more than 30 days was 0.2 ± 0.3 times per month per patient (range, 0–1.9 times per month). Device-related infections at various locations were observed in 42 patients (68.9%). Blood culture was positive at least once in 36 patients (59.0%). Ten patients (16.4%) underwent reoperation for mediastinitis. Inflow/outflow cannula exit site infection was observed in 19 patients (31.1%). The infection-free curve is shown in Fig. 3C. Although the infectious events occurred most frequently in the first 6 months after LVAS implantation, events continued to occur thereafter. The infection-free rate improved significantly by year of implantation (P = 0.0464, log rank test). Among the preoperative and operative parameters, early operation (before 2003) and reoperation were the independent risk factors for device-related infections as determined by multivariate analysis using the Cox hazard model (Table 5). Tracheostomy was required in 20 patients (32.8%) and temporary hemodialysis in 25 (41.0%).

The most common cause of death was a cerebrovascular event (Table 6). Ten patients (16.4%) died due to cerebral infarction and nine (14.8%) died because of cerebral bleeding. Multiple organ failure (MOF) and sepsis, already

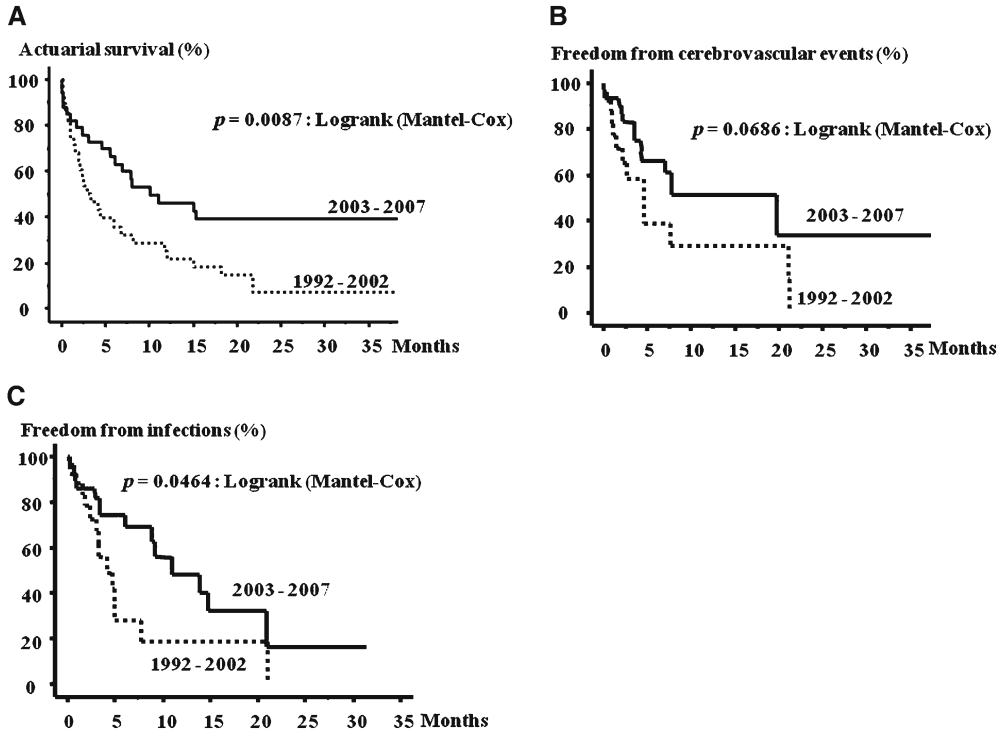

Fig. 3. **A** Actuarial survival for patients being implanted with a LVAS in the past 5 years and for those receiving a LVAS in previous years. **B** Cerebrovascular event-free curve and **C** device-related infection-free curve

Table 3. Risk factors for right heart failure (Cox hazard model)

Variables	Univariate	Multivariate	
	P value	*P* value	Odds ratio (95% CI)
Sex (female)	0.1500		
Date of implantation (~2002)	**0.0235**		
Diagnosis (idiopathic)	0.1857		
ECMO	**0.0012**	**0.0121**	**48.017 (2.336–986.913)**
Intubation	**0.0347**		
Blood pressure	0.2530		
Creatinine	0.1115	**0.0408**	**2.680 (1.042–6.892)**
AST	0.0722		
Total bilirubin	0.0967		
CRP	0.2589		
Inflow site (left atrium)	**0.0150**		

Preoperative parameters and operative procedures were analyzed and the entry probability was set at 0.30
Bold indicates statistical significance
CI, confidence interval

Table 4. Risk factors for cerebrovascular events (Cox hazard model)

Variables	Univariate	Multivariate	
	P value	*P* value	Odds ratio (95% CI)
Date of implantation (~2002)	**0.0218**	0.5451	1.533 (0.384–6.120)
Diagnosis (ischemic)	0.1611		
Prothrombin time	0.1711		
Ejection fraction	0.2224		
Inflow site (left atrium)	**0.0095**	0.1460	2.671 (0.710–10.043)

Preoperative parameters and operative procedures were analyzed and the entry probability was set at 0.30

Table 5. Risk factors for device-related infections (Cox hazard model)

Variables	Univariate	Multivariate	
	P value	*P* value	Odds ratio (95% CI)
Sex (male)	0.1453		
Date of implantation (~2002)	**0.0033**	**0.0025**	**5.687 (1.842–17.554)**
Diagnosis (ischemic)	0.0830		
Intubation	**0.0472**	0.3783	0.337 (0.030–3.795)
Intra-aortic balloon pump	0.2586		
ECMO	0.1423		
Blood pressure	0.1349		
Total protein	0.2072		
Prothrombin time	0.2992		
CRP	0.1354		
LVDd	0.0925		
Reoperation	0.0652	**0.0328**	**4.702 (1.135–19.489)**

Preoperative parameters and operative procedures were analyzed and the entry probability was set at 0.30

Table 6. Cause of death

	No. of patients (%)
Sepsis	12 (19.7)
Cerebral infarction	10 (16.4)
Cerebral bleeding	9 (14.8)
Multiple organ failure	9 (14.8)

present preoperatively in the majority of cases, were the other leading causes of death. Nine patients (14.8%) died of MOF and 12 (19.7%) died of sepsis. Among the preoperative and operative parameters, age at implantation, early operation (before 2003), the need for right heart support to withdraw cardiopulmonary bypass, and the cardiopulmonary bypass time were significant risk factors for death as assessed by univariate analysis using the Cox hazard model. Multivariate analysis revealed that early operation (before 2003) and the need for right heart support were independent risk factors for patient survival after LVAS implantation (Table 7).

Discussion

The Toyobo paracorporeal LVAS is the only LVAS that has been commercially available for a long time in Japan. The device is similar to the other paracorporeal LVASs developed and used in the United States and European countries. McBride et al. reported the clinical outcomes of 111 patients supported by the Thoratec LVAS.[9] They divided the patients into bridge-to-transplantation and bridge-to-recovery groups and analyzed them separately. In the bridge-to-transplantation group, the actuarial survival curve dropped rapidly in the first month of LVAS support, as in our study, but survival at 1–5 years was more than 50% due to the good results of transplantation. Fifty-eight percent of the patients in this group underwent transplantation and were discharged from hospital. Results for the bridge-to-recovery group were not as good and less than 30% survived for 1 year. Schmid et al. also reported excellent results with the Excor LVAS (Berlin Heart, Berlin, Germany).[10] They used the Excor system in 29 consecutive patients, including children, as a LVAS or a biventricular VAS, and the 1-year survival was more than 70%. The mean duration of support was 135 ± 117 days and 14 of the 29 patients (48.3%) underwent heart transplantation. In our study, the mean duration of support (224 ± 283 days) was much longer than that reported by Schmid et al., but only five of our patients (7.7%) were able to undergo heart transplantation. The 1-year survival rate of our patients in the past 5 years has been about 50% (Fig. 3A). One of the main reasons for the discrepancy between the survival when using the Excor system and the Toyobo LVAS may be the extreme shortage of heart donors in Japan.

In the United States and in European countries, the device is generally selected based on the expected duration of support. Paracorporeal LVAS is used mainly for short- to mid-term support of up to 6 months, and if a longer duration of support is expected, an implantable LVAS is selected. However, the Toyobo LVAS is currently the only commercially available LVAS in Japan. We have no choice but to use this LVAS for long-term support in the majority of patients. In Japan, Novacor and HeartMate LVASs have been used in selected institutes for a limited period, and the HeartMate XVE is now under consideration for commercial use. Clinical trials using the EvaHeart (SunMedical Technology Research, Nagano, Japan), Jarvik2000 (Jarvik Heart, New York, NY, USA), and DuraHeart (Terumo, Tokyo, Japan) are currently ongoing. The new devices are often implanted in selected patients who have no significant complications. As a result, the Toyobo LVAS has been implanted in the most critically ill patients, often in emergent situations. In the present series, ECMO support was required preoperatively in 49% of the patients, whereas it was required in only 21% of patients in McBride's Thoratec study[9] and in 34% in the Schmid's Excor study.[10] Other organ dysfunction was also present in a high percentage of patients in our series. These could be the main cause of early mortality in our patients and were the other main reasons for the worse survival rates in Japan.

Thromboembolism and device-related infections are the most frequent and often fatal complications in patients

Table 7. Risk factors for death (Cox hazard model)

Variables	Univariate	Multivariate	
	P value	*P* value	Odds ratio (95% CI)
Age	**0.0236**	0.2616	1.027 (0.980–1.076)
Date of implantation (~2002)	**0.0062**	**0.0067**	**7.635 (1.756–33.197)**
Body surface area	0.1390		
Intubation	0.2250		
AST	0.2807		
ALT	0.2779		
Total bilirubin	0.2859		
Brain natriuretic peptide	0.2863		
Inflow site (left atrium)	0.2828		
Right heart support	**0.0104**	**0.0220**	**7.943 (1.348–46.786)**
Cardiopulmonary bypass time	**0.0300**	0.8098	0.998 (0.983–1.014)

Preoperative parameters and operative procedures were analyzed and the entry probability was set at 0.30

under LVAS support. We experienced cerebral bleeding in 16 patients (26.2%) and cerebral infarction in 19 patients (31.1%). In some of the 16 patients with cerebral bleeding, the hemorrhage might have been preceded by infarction (postinfarct hemorrhage), which was difficult to distinguish from primary hemorrhage. Another important complication was infection of the inflow/outflow cannula exit site. This infection was often observed when patients started to move their body freely after their general condition improved. It is known that the individual risk for an inflow/outflow cannula exit site infection (driveline infection in cases of implantable LVAS) increases with the duration of support and it reaches up to 94% at 1 year in other reports.[11] This complication also has a significant influence on patient survival.[11] Although it did not always result in systemic infection in our study, the patients' quality of life was significantly reduced by the pain and unpleasant smell.

Among preoperative and operative parameters, early operation (before 2003) and the requirement of right heart support to withdraw the cardiopulmonary bypass were independent risk factors for survival as assessed by multivariate analysis. Preimplantation hemodynamic criteria did not predict the outcome of patients receiving circulatory support, as shown in previous studies.[12,13] Early-period operation was also detected as an independent risk factor for device-related infections. Improvement in postoperative management, including infection control, could have lead to better patient survival.

It is known that right heart failure occurs in approximately 15%–20% of patients postoperatively.[14–16] The causes for right heart failure are multifactorial and, in many instances, right heart failure becomes clinically evident only after LVAS support has been initiated.[17] Researchers from Cleveland Clinic reported that preoperative circulatory support was one of the independent risk factors for right heart failure by multivariate analysis,[18] which is compatible with our findings. Our finding was also compatible with that of Dang et al., who reported a higher mortality rate and lower bridge-to-transplantation rate in patients with right heart failure.[17] Although the rationale for the use of biventricular VAS has been questioned because of the high mortality rate in patients undergoing biventricular VAS implantation,[19] Tsukui et al. recently reported excellent outcomes with biventricular VAS for morbid congestive heart failure.[20] In their report, overall survival was 69%, and about half of the recent patients could be discharged from the hospital with biventricular VAS, but again, their patients underwent transplantation 86 days after the VAS operation on average. Long-term management with biventricular VAS is problematic because of the higher frequency of embolic events not only in the systemic circulation but also in the pulmonary system.

As LVAS management becomes more sophisticated with meticulous postoperative management protocols, more and more patients under Toyobo LVAS support are surviving for a long time on the device. In the present study, 22 patients (36.1%) were supported by the Toyobo LVAS for more than 6 months and 13 patients (21.3%) for more than 1 year. The patients' quality of life is currently an issue that cannot be ignored. Since this device was designed for a hospital setting, no patient has been discharged on this device so far. However, a recently developed portable driver, Mobart NCVC (Nipro, Tokyo, Japan), enables patients to walk around by themselves. Hospital discharge may become possible with the portable driver, as with the Thoratec LVAS in the United States.[21]

We have reported our 15 years of experience with the Toyobo paracorporeal LVAS. Although the rate of device-related morbidity was significant, the Toyobo LVAS can provide improving survival and durable support for a duration much longer than that with other paracorporeal LVASs used in other countries. Considering the current severe shortage of heart donors in Japan, the use of other smaller implantable devices should be approved for long-term support. Nevertheless, paracorporeal devices will still play an important role in supporting biventricular failure patients or potentially recoverable candidates. The use of LVAS as a bridge to recovery for chronic heart failure is also attractive. Strategies for multidisciplinary treatment combining the LVAS with other modalities such as cardiac resynchronization therapy[22] or myocardial regenerative therapies[23] may be important to achieve this goal.

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