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Durable Ventricular Assist Device for Bridge to Transplantation

Minoru Ono

Abstract

A durable ventricular assist device (VAD) is a key mechanical circulatory support to safely bridge a heart transplant candidate to transplantation over a long waiting period. Recent UNOS policy change has a great impact on the role of continuous-flow VAD as a bridging device. The rest of the majority of countries still rely on a cf-VAD as a safe and effective support device. A sole durable VAD for bridge to transplantation in pediatric patients is Berlin Heart EXCOR, for which there is a growing demand through the improvement of a long-term result. In this chapter, I will overview the history and the present status of durable VAD for bridge to transplantation in both adult and pediatric patients.

Keywords: heart transplantation, ventricular assist device, bridge to transplantation

1. Introduction

The first bridge to transplantation strategy was started in the 1980s, but a patient needed to stay in hospital due to a huge driving console, even if the device was implantable. First-generation of implantable ventricular assist device (VAD) was not widely implanted due to its huge size and a limited reliable support period. Development and introduction to the clinical arena of a rotary blood pump in the early 2000 completely changed the landscape. The smaller pump size enabled easier implantation in smaller body size patients and an operation of the device by portable batteries paved a way to outpatient management. A so-called second-generation device is driven in the presence of contact bearings, which were found to lead to several tough complications, such as pump thrombosis and gastrointestinal bleeding. Advent of the third-generation device, in which an impeller is rotated without contact to an inner housing by magnetic and/or hydrodynamic levitation systems. Most updated devices are manufactured by incorporating a magnetic levitation system. Thanks to these technological refinements and improvements of continuous-flow VAD (cf-VAD) support patients, the survival of patients on a VAD has been steadily prolonging. In this chapter, the current status and survival of cf-VAD patients for bridge to transplantation (BTT) in Japan and the United States (US) are reviewed.

2. Bridge to transplantation in Japan: analysis of J-MACS report

Two Japan-made cf-LVAD (EVAHEART, Sun Medical Research Corp., Nagano, Japan and DuraHeart, Terumo Heart Inc., Ann Arbor, MI) were approved for health insurance coverage as a BTT in April 2010. Subsequently, HeartMate II (Abbott, Chicago, IL) in April 2013, Jarvik 2000 (Jarvik Heart Inc., New York, NY) in January 2014, HVAD (Medtronic, Minneapolis, MN) in February 2019 and HeartMate 3 (Abbott, Chicago, IL) in July 2019 were approved for a BTT. Similar to Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) in the US, we have the Japanese Registry for Mechanically Assisted Circulatory Support (J-MACS) as a mandatory registry system of cf-LVAD. J-MACS was established in 2009 with an intention of harmonization by doing with Food and Drug Administration (FDA) in the US [1].

Registry summary report is published every year, and the most recent one was published online in March 2021 [2]. HeartMate 3 was approved as the first DT device in May 2021, so the most recent J-MACS registry report included solely data regarding a BTT strategy. This report analyzed data of cf-LVADs which were implanted by October 31, 2020. The total number of implantation was 1353, among which primary implantation was in 956 (70.7%), bridge to bridge (BTB, conversion from paracorporeal device to cf-LVAD) in 218 (16.1%) and device exchange from cf-LVAD in 179 (13.2%). The total number of patients was 1174 (primary VAD + BTB). There were 871 male patients (74.2%) with an average age of 43.5 years. The distribution of the age in decade is shown in **Table 1**. The height, weight, body mass index (BMI) and body surface area (BSA) were 167.0 +/- 8.7 cm, 57.6 +/- 11.8 kg, 20.5 +/- 3.3 kg/m² and 1.64 +/- 0.19 m², respectively (**Table 2**). The majority of the patients were implanted for non-ischemic dilated cardiomyopathy (DCM; 64.8%), followed by ischemic heart disease (12.2%) and dilated-phase of hypertrophic cardiomyopathy (10.6%) (**Table 3**). The severity INTERMACS/J-MACS profile of the patients before cf-LVAD implantation was shown in **Table 4**. Almost half of the patients were implanted at profile 3 (46.7%), and only 9.1% belonged to profile 1. Kaplan–Meier survival curve showed that 1- and 2-year survival rates were 92% and 89% (**Figure 1**). The longest support exceeded 5 years.

		N	%
Total number		1174	
Gender	Male	871	74.2
	Female	303	25.8
Age distribution	< 10	1	0.1
	10–19	66	5.6
	20–29	129	11.0
	30–39	227	19.3
	40–49	307	26.1
	50–59	304	25.9
	60–69	139	11.8
	> 70	1	0.1

Table 1.
Gender and age distribution.

	Mean ± SD
Age (years)	43.5 ± 13.4
Height (cm)	167.0 ± 8.7
Weight (kg)	57.6 ± 11.8
BMI (kg/m ²)	20.5 ± 3.3
BSA (m ²)	1.64 ± 0.19

Table 2.
Patient demographics. BMI: Body mass index, BSA: Body surface area.

	N	%
CHD	22	1.9
IHD	143	12.2
HCM (dilated phase)	125	10.6
HCM (no dilated phase)	5	0.4
VHD	10	0.9
DCM	761	64.8
RCM	5	0.4
Others	102	8.7
Unknown	1	0.1
Total	1174	

CHD: congenital heart disease, IHD: ischemic heart disease, HCM: hypertrophic cardiomyopathy, VHD: valvular heart disease, DCM: idiopathic dilated cardiomyopathy, RCM: restrictive cardiomyopathy.

Table 3.
Causative diseases.

INTERMACS/J-MACS profile	N	%
Profile 1	107	9.1
Profile 2	453	38.6
Profile 3	548	46.7
Profile 4	52	4.4
Profile 5–7	14	1.2
Total	1174	

Table 4.
Preimplant INTERMACS/J-MACS profile.

Figure 2 shows Kaplan–Meier survival stratified by the age group by decade. Patients with age in 50s and over 60 years had significantly worse survival ($p < 0.0001$). **Figure 3** shows the survivals divided by preoperative J-MACS profiles, demonstrating a significantly worse survival in profile 1 ($p = 0.032$). **Figure 4** shows the competing

Figure 1.
Actuarial survival after BTT cf-LVAD implantation.

Figure 2.
Actuarial survival after BTT cf-LVAD implantation stratified by age group.

outcomes. Waiting time for heart transplantation is more than 4 years recently, so the curve of survival on the device crosses that of transplantation around 1500 days.

Pump thrombosis-free curve is shown in **Figure 5** with 1- and 2-year event-free rates of 97% and 97% for the primary implant, which is much less compared to an INTERMACS report. Driveline infection-free curve is shown in **Figure 6**, demonstrating that 1- and 2-year event-free rates are 78% and 67% for a primary implant.

Figure 3.
Actuarial survival after BTT cf-LVAD implantation stratified by preimplant profiles.

Figure 4.
Competing outcomes.

Figure 7 shows stroke-free curve including all stroke events of any grade. The gastrointestinal bleeding-free curve is shown in **Figure 8**, demonstrating 1- and 2-year event-free rate of 95% and 93% for primary implantation, which is much more infrequent compared to the US. **Figure 9** shows the readmission-free rate. Almost two-thirds of the patients were readmitted within 1 year and three-quarters in 2 years, which is still an important issue to be solved. **Figure 10** shows a pump exchange free rate with a 1- and 2-year event-free rate of 96% and 92% for primary implantation.

Figure 5.
Pump thrombosis-free rate divided by primary VAD and BTB.

Figure 6.
Driveline infection-free rate divided by primary VAD and BTB.

3. Heart transplantation in Japan: analysis of heart transplantation registry

Five hundred sixty-six heart transplantations (512 adult and 54 pediatric HTx) were performed by December 2020 in Japan since the Organ Transplantation Act came into force in October 1997 [3]. **Figure 11** shows the number and the type of circulatory support device on which the recipient was placed at the time of HTx [4]. There were only three recipients who were not on any circulatory support including inotropes. All these

Figure 7.
Stroke (any grade)-free rate divided by primary VAD and BTB.

Figure 8.
Gastrointestinal bleeding-free rate divided by primary VAD and BTB.

three were pediatric patients. Thirty-two recipients (5.7%) were on continuous inotropic support. Thus, the majority of the recipients (93.8%) were on any type of mechanical circulatory support. Paracorporeal air-driven LVAD was used in 126 patients (22.3%), including 110 Nipro VAD (Nipro, Osaka, Japan) and 16 Berlin Heart Excor pediatric VADs (Berlin Heart GmbH, Berlin, Germany). Implantable LVAD was used in 393 recipients (69.4%) and 12 patients (2.1%) were on biventricular VAD (BIVAD) support. Most frequently implanted cf-LVAD device was HeartMate II in 166, followed by EVAHEART in 86, Jarvik 2000 in 61, DuraHeart in 56 and so on. A small number of first-generation implantable pulsatile devices were used in the early years (n = 11).

Figure 9.
Readmission-free rate divided by primary VAD and BTB.

Figure 10.
Pump exchange-free rate divided by primary VAD and BTB.

Figure 12 shows a yearly trend of the type of circulatory support [4]. Paracorporeal VADs were mainly used for a BTT before the year 2011 when two Japan-made cf-LVAD were approved for health insurance coverage. Berlin Heart Excor pediatric was started to be covered by health insurance in 2015. **Figure 13** shows a yearly trend of waiting time for HTx divided by adult and pediatric recipients [4]. Since a shortage of brain-dead donations is extreme in Japan, a waiting time has continuously prolonged and reached 1625 days in adult recipients in 2020. A waiting time was variable year by year in pediatric recipients, but in general longer than that of Western countries.

Figure 11.
The number and the type of circulatory support at HTx (n = 566). Cf-VAD: continuous-flow left ventricular assist device, PI VAD: pulsatile implantable left ventricular assist device, P-LVAD: paracorporeal left ventricular assist device.

Figure 12.
The number and the type of circulatory support at HTx in each year. Cf-VAD: continuous-flow left ventricular assist device, PI VAD: pulsatile implantable left ventricular assist device, P-LVAD: paracorporeal left ventricular assist device.

4. Impact of bridge to transplantation on the results of heart transplantation: from ISHLT registry report

A cf-VAD has been widely used for a BTT in these two decades due to improvement of long-term safe support, less complications and size miniaturization. **Figure 14** is from ISHLT (International Society for Heart and Lung Transplantation) 2019 Annual Report Slides [5], showing an annual trend of a ratio of adult patients who were bridged to HTx with mechanical circulatory support devices. Including LVAD, BIVAD, VAD + ECMO and isolated RVAD, 52.5% and 49.6% of the recipients were bridged to HTx in 2016 and 2017, respectively. An isolated LVAD support was the

Figure 13.
Waiting time for heart transplantation in both adult and pediatric recipients.

Figure 14.
Adult heart transplants. The ratio of patients bridged with mechanical circulatory support by year and device type.

majority like 49.6% and 47.0% in 2016 and 2017, respectively. **Figure 15** from ISHLT 2019 Report demonstrates that survival (89.9% and 77.6% at 1 and 5 years) in patients with cf-LVAD support is identical with that of no LVAD/no inotrope group (90.0% and 79.0%) or no LVAD/Inotrope group (91.9% and 78.7%) [5]. Cox-hazard analysis of risk factors for 1-year mortality among adult heart transplants between 2012 and June 2017 showed that VAD support was a significant risk factor ($p < 0.01$; HR 1.241, 95% CI 1.082–1.424). However, VAD bridge was not a significant risk factor for cardiac allograft vasculopathy (CAV) or severe renal dysfunction within 5 years by Cox-hazard analysis of adult heart transplants conditional on survival to discharge between 2008 and June 2013 [5].

Figure 16 from ISHLT Pediatric HTx 2019 Annual Report shows an annual trend of a ratio of patients who were bridged with mechanical circulatory support [6]. Different from adult recipients, an increasing trend of the MCS bridge ratio was not steady, but there was a trend for increase with 31.8% in VAD or TAH and 1.5% in VAD + ECMO. **Figure 17** demonstrates that about a quarter of pediatric

Figure 15. Adult heart transplants. Kaplan–Meier survival by pre-transplant mechanical circulatory support use (transplants: Jan 2010 –June 2017).

Figure 16. Pediatric heart transplants. Ratio of patients bridged with mechanical circulatory support by year (transplants: Jan 2005 –Dec 2017).

Figure 17. Pediatric heart transplants. The ratio of patients bridged with mechanical circulatory support by the device (transplants: Jan 2010 –June 2018).

Figure 18. Pediatric heart transplants. The ratio of patients bridged with mechanical circulatory support by age group (transplants: Jan 2010 –June 2018).

Figure 19. Pediatric heart transplants. Kaplan–Meier survival by mechanical circulatory support usage (transplants: Jan 2010 –June 2017).

recipients were bridged with LVAD (20.2%) or BIVAD (5.4%) between 2010 and June 2018 [6]. Notably, almost a half of the recipients were bridged with LVAD (39.8%) or BIVAD (8.7%) in DCM among transplants between 2010 and June 2018 [6]. **Figure 18** shows a ratio of patients who were bridged with MCS divided by age group [6]. A total of 30% patients with age of 1 to 17 years were bridged with VAD or TAH, or VAD + ECMO [6]. **Figure 19** is a Kaplan–Meier survival curve stratified by device strategies, demonstrating that survivals of the VAD or TAH group (93.7% and 85.2% at 1 and 5 years) are not different from those of no support group (93.1% and 84.8%) [6]. The VAD support was a risk factor for 1-year mortality by Cox-hazard analysis ($p = 0.02$; HR 1.396, 95% CI 1.047–1.860). However, as in adult HTx, pretransplant VAD use was not associated with CAV progression or renal dysfunction within 5 years conditional on survival to discharge.

5. Most recent publications on bridge to transplantation

In addition to BTT, a cf-VAD has been implanted for bridge to candidacy or destination therapy. A recent trend of survival after cf-VAD implantation for each strategy was reported in The Society of Thoracic Surgeons (STS) INTERMACS 2020 annual Report [7]. Survival of cf-LVAD patients by a device strategy is shown in **Figure 20**. Patients with a BTT strategy enjoyed better survival than those with other strategies. The absolute difference of survival at each year between BTT and DT strategies ranged from 6.7% to 10.3%. Steady improvement of survival after HTx with cf-VAD support was clearly demonstrated in the ISHLT adult heart transplantation 2021 report [8]. As shown in **Figure 21**, a significant improvement in survival is achieved as years elapsed. A similar finding was also confirmed in pediatric recipients with a BTT strategy [9].

A new heart allocation policy was introduced in October 2018 with an intention to: 1. decrease a wait-list death, and 2. equalize a chance to be transplanted for a severely ill recipient. This policy change made the new donor heart allocation system to prioritize candidates supported by temporary devices. However, waitlist and post-transplant outcomes in candidates with durable LVAD remain to be elucidated. Mullan et al. analyzed the United Network for Organ Sharing (UNOS) database of adults with cf-LVAD at listing or implanted while listed between April 2017 and April 2020, and elucidated that the number of patients listed with LVAD decreased nationally over time from 102 in April 2017 to 12 in April 2020 ($p < 0.001$). The proportion of patients with LVAD at the time of transplant decreased from 47% to 14% (**Figure 22**) [10]. They also showed that transplantation rates were not different before and after the allocation policy change (85.4% vs. 83.6%; $p = 0.225$), but waitlist time decreased in the post-period (82 vs. 65 days; $p = 0.004$). Waitlist survival did not change, but post-transplantation survival was worse in patients with BTT post-change ($p < 0.001$) [10]. Abrupt decrease of a BTT strategy among cf-LVAD implantation was endorsed by the STS INTERMACS 2020 annual Report (**Figure 23**) [7].

Edelson et al. conducted an ISHLT data analysis to seek the influence of mechanical circulatory support on post-transplant outcomes in pediatric patients [11]. Among

Figure 20. Kaplan–Meier survival curves for primary cf-LVAD for 2015–2019 by implant strategy. BTC: Bridge to candidacy, BTT: Bridge to transplant, Cf-LVAD, continuous-flow left ventricular assist device, DT: Destination therapy.

Figure 21.
Adult heart transplants with *cf*-VAD BTT. Kaplan–Meier survival within 12 months by recipient era (transplants: Jan 2000 –Jun 2017).

Figure 22.
Trends in LVAD utilization in patients listed for heart transplantation.

5095 patients between 2005 and 2017, 26% of patients received MCS prior to transplant: 240 (4.7%) on extracorporeal membrane oxygenation (ECMO), 1030 (20.2%) on VAD, and 54 both. They found that survival in congenital heart disease (CHD) and DCM was similar in patients with no MCS or those with VAD, while pretransplant ECMO use is strongly associated with death after transplant particularly in children with CHD. HTx in patients with Fontan operation has been challenging, and a durable LVAD has been used to bridge a post-Fontan patient anecdotally. The first collective study of durable VAD support in Fontan patients was reported in 2021. Cedars

Figure 23.
Implant strategy by implant year for primary continuous-flow LVADs.

et al. conducted a retrospective analysis of data collected in the Advanced Cardiac Therapies Improving Outcomes Network (ACTION) registry, a multicenter learning network of pediatric hospitals actively involved in the implantation and management of VADs in children and adults with CHD [12]. They identified 45 Fontan patients implanted with a VAD. The average age of patients was 10 years (interquartile range: 4.5–18). The majority of patients were INTERMACS Profile 2 (56%). The most commonly employed device was the Medtronic HVAD (56%). A total of 13 patients were discharged on device support, and 67% of patients experienced adverse events, the most common of which were neurologic (25%). At 1 year after device implantation, the rate of transplantation was 69.5%, 9.2% of patients continued to be VAD supported, and 21.3% of patients had died.

6. Conclusions

In this chapter, the author reviews durable VAD used for a BTT. BTT strategy both in adult HTx by cf-LVAD and in pediatric HTx by Berlin Heart Excor or cf-LVAD is mandatory in Japan because a waiting time is over 4 years in adults and over 2 years in children due to a severe donor shortage. A total of 95% of adult HTx and 80% of pediatric HTx were bridged with a durable LVAD as of December 2020. As shown by J-MACS registry data, the survival of cf-LVAD patients was favorable. In the majority of European countries and the US cf-VAD use for a BTT was steadily increasing. VAD support was employed successfully in about 50% in adult and about 30% in pediatric HTx recipients. Survival after HTx with durable VAD support has been improving, and no survival difference is observed compared to that of recipients without VAD support. Recent heart allocation policy change in the US had a great impact on a judgment to choose a durable LVAD for a BTT. A chance to choose BTT strategy by using cf-LVAD will be declining undoubtedly, but nobody still knows what will be a future outcome.

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Author details

Minoru Ono

Department of Cardiovascular Surgery, The University of Tokyo, Tokyo, Japan

*Address all correspondence to: ono-tho@h.u-tokyo.ac.jp

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