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Optimal timing of heart transplantation in patients with an implantable left ventricular assist device

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Heart transplantation (HTPL) has been established as the gold-standard surgical treatment for end-stage heart failure. However, the use of a left ventricular assist device (LVAD) as a bridge to HTPL has been increasing due to the limited availability of HTPL donors. Currently, more than half of HTPL patients have a durable LVAD. Advances in LVAD technology have provided many benefits for patients on the waiting list for HTPL. Despite their advantages, LVADs also have limitations such as loss of pulsatility, thromboembolism, bleeding, and infection. In this narrative review, the benefits and shortcomings of LVADs as a bridge to HTPL are summarized, and the available literature evaluating the optimal timing of HTPL after LVAD implantation is reviewed. Because only a few studies have been published on this issue in the current era of third-generation LVADs, future studies are needed to draw a definite conclusion.

Keywords: Transplantation; Ventricular assist device; Outcomes

INTRODUCTION

The number of patients who suffer from end-stage heart failure (ESHF) is rapidly increasing in many countries, including Korea. The estimated number of ESHF patients in Korea was over one million in 2018 and the prevalence increased from 0.77% in 2002 to 2.24% in 2018 [1]. Although heart transplantation (HTPL) has been established as the gold standard surgical treatment for ESHF, limited donor availability is still the major hurdle in expanding its indications, and the annual number of patients undergoing HTPL has plateaued since 1990 [2].

The National Institute of Health in the United States started an artificial heart program in 1964, and the first-generation model of the left ventricular assist device (LVAD) received an Investigational Device Exemption (IDE) from the Food and Drug Administration (FDA) for use as a bridge to transplant (BTT) in 1985 [3]. With advances in LVAD technology, overall survival in ESHF patients waiting for HTPL has been improving [4], and there has been a resultant increase in the number of patients undergoing HTPL with a BTT LVAD [5].

However, LVADs have limitations, and the optimal timing of HTPL in patients with LVADs is still up for debate [6,7]. Therefore, this article was conducted to review the benefits and shortcomings of LVADs as a BTT and to investigate the current evidence regarding the optimal timing of HTPL in patients with BTT LVADs.

HIGHLIGHTS

- The timing of transplantation after ventricular assist device implantation is debatable.
- At least 1 month of support may be needed before heart transplantation.
- Three months of support may be beneficial for improving functional status.
- Delayed transplantation at over 1 or 2 years after ventricular assist device implantation may be harmful.

BENEFITS OF THE LEFT VENTRICULAR ASSIST DEVICE

The first LVAD that was approved for BTT by the FDA was the HM IP 1000 (Thoratec Corp.), a first-generation LVAD with a pulsatile pneumatic pump device [3]. Historical trials [8,9] showed that first-generation LVADs were more beneficial compared to optimal medical therapy (OMT) for patients waiting for HTPL. A previous study [8] found that patients with HM IP 1000s had a greater chance of being successfully transplanted than those with OMT (71% [53 of 75 patients] vs. 36% [12 of 33 patients]). Moreover, the 1-year survival rate after HTPL was significantly higher in the LVAD group than in the OMT group (91% vs. 67%). Another study [9] compared the results of 288 patients who had HeartMate Vented Electric (Thoratec Corp.) LVADs with those of 48 historical control patients with OMT. The results of the latter study were similar to those of the former, including a significantly higher proportion of patients who underwent HTPL and a significantly higher survival rate after HTPL in the LVAD group than in the OMT group. These improved results after BTT LVAD implantation in patients with ESHF awaiting HTPL could be explained by several factors. The theoretical advantage of the LVAD for BTT is that the patient's condition could be optimized for HTPL by the LVAD as follows: (1) improvement in end-organ perfusion, (2) improvement in functional status by ambulating and gaining strength, and (3) increased probability of participating in cardiac rehabilitation [10].

With the proven efficacy of LVADs and the introduction of second- and third-generation LVADs with improved device designs, the number of patients who underwent LVAD in the United States increased from 98 patients in 2006 to more than 2,000 patients in 2014, and a total of more than 24,000 patients underwent LVAD implantation between 2006 and 2017 [10,11]. As the number of patients with an LVAD increases, the proportion of patients who undergo HTPL after LVAD therapy is also increasing. Currently, almost half of HTPL patients have a history of LVAD for BTT [5].

SHORTCOMINGS OF LEFT VENTRICULAR ASSIST DEVICES

Although LVADs have been used to rescue patients with ESHF who either could not wait until HTPL or were not candidates for HTPL, LVADs also have shortcomings. In the current era of third-generation as well as second-generation LVADs, which are characterized by continuous flow (CF) with centrifugal pumps and axial pumps, respectively, the loss of pulsatility has been identified as one of the major drawbacks of LVAD therapy. Loss of pulsatility generates many harmful effects on the patient's body that result in long-term complications of LVAD therapy, such as gastrointestinal bleeding, hypertension, stroke, and pump thrombosis [12].

In addition to the loss of pulsatility, other issues such as hemocompatibility and device size (although it is getting smaller) are major hurdles that must be overcome. Finally, a fully implantable device is needed not only to improve convenience for patients but also to reduce serious complications after LVAD implantation; because the driveline passes through the patient's body and connects to an external module, it is prone to causing infection and mechanical failure. Driveline infection is one of the most common complications after LVAD implantation, and the reported incidence ranges from 2.9% to 29% [13]. These shortcomings of the LVAD may worsen patient outcomes if the duration of the LVAD is prolonged while awaiting HTPL.

OPTIMAL TIMING OF HEART TRANSPLANTATION AFTER LVAD IMPLANTATION

Evidence in the Era of Second-Generation Devices

Due to the theoretical advantages and drawbacks described above, many studies have been conducted to determine whether there is an optimal timing of HTPL after LVAD implantation in which patients receive maximum

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benefits from LVAD support while minimizing harmful effects. Most studies enrolled patients who underwent LVAD implantation using a second-generation device, particularly HeartMate 2 (Abbott Laboratories). A previous study provided some answers to one of the important questions regarding the duration required to obtain a theoretical advantage from the LVAD [6]. In this study, the authors enrolled 1,332 patients who were registered in the United Network for Organ Sharing (UNOS) between 2011 and 2012. The patients were divided into three groups according to the duration of the LVAD before HTPL: <90 days (n=130), 90–365 days (n=729), and >365 days (n=473). They analyzed the survival rate and functional status of the patients at both the time of LVAD implantation and the time of HTPL. Functional status was graded by the Karnofsky Performance Scale [14], and proportions of patients needing complete assistance were evaluated. Study results showed that LVAD support for 90 days or more was associated with improvements in pretransplant functional performance. However, the duration of LVAD support before HTPL did not significantly affect posttransplant morbidity or mortality. Other studies also demonstrated that the LVAD duration did not affect posttransplant survival in the era of second-generation CF-LVADs [7,15]. One study analyzed 250 HTPL patients from 468 patients with LVADs at 36 centers in a multicenter trial [7]. The authors divided patients into four groups based on LVAD duration (<30 days, 30–89 days, 90–179 days, and ≥180 days). They showed that overall, 30-day, and 1-year survival rates were not significantly different between the groups. In another study [15] in which the patients were grouped by the cutoff of 180 days, the authors also showed that there were no significant differences in overall survival up to 5 years after HTPL. On the contrary, other studies have shown a significant impact of LVAD duration on posttransplant survival [16]. In this study, the authors analyzed 122 patients who successfully underwent HTPL after BTT LVAD implantation. The cutoff duration in that study was 1 year after LVAD implantation. The study results demonstrated that prolonged support time over 1 year was associated with a worse 3-year survival as well as in-hospital mortality (Table 1).

Evidence in the Current Era of Third-Generation Devices

Because there are fundamental differences in device design and expected risks of complications between second- and third-generation LVADs, the study results based on second-generation LVADs may not provide important clinical perspectives in the current era of third-generation LVADs.

Table 1. Summary of findings demonstrating the significant impact of the duration of left ventricular assist device usage on heart transplantation outcomes

Study	Operative era	Country	Study population			Device used	Cutoff duration at risk	Outcome measure	Result
			Total	Study group	Control group				
Grimm et al. (2016) [6]	2011–2012	USA	1,332	130	1,202	CF-LVAD in 85%–90% of patients	<90 day	Changes in functional status[a)]	40.8%–43.1% vs. 34.6%–25.0%
Takeda et al. (2015) [16]	2004–2013	USA	122	32	90	HeartMate II	≥1 yr	3-yr survival	88% vs. 68%
Fukuhara et al. (2016) [17]	2011–2014	USA	1,857	267	1,590	HeartMate II (85.6%) HVAD (13.1%) Others (1.3%)	>2 yr (ref. <1 yr)	30-day survival 2-yr survival	92.9% vs. 96.4% 78.9% vs. 88.2%
Brown et al. (2019) [18]	2009–2014	USA	1,186	28	1,158	Not specified	<31 day	3-yr mortality	2.50 (1.22–4.76)[b)] 2.26 (1.25–5.26)[c)]
Truby et al. (2018) [19]	2009–2017	USA	263	-	-	CF-LVAD	>1 yr	Severe primary graft dysfunction	HR, 2.48; 95% CI, 1.14–5.40
Yu et al. (2022) [20]	2009–2019	Taiwan	95	23	74	Not specified[d)]	<24 day	5-yr survival	62% vs. 81%

CF, continuous flow; LVAD, left ventricular assist device; HVAD, HeartWare Ventricular Assist Device; HR, hazard ratio; CI, confidence interval.

[a)]Proportion of patients with worse performance cohort needing complete assistance assessed with Karnofsky Performance scale; [b)]HR with 95% CI compared to support duration of 31 to 365 days; [c)]HR with 95% CI compared to support duration >365 days; [d)]Included both temporary and durable LVADs.

The characteristics of the third-generation LVADs, namely the HeartWare Ventricular Assist Device (HVAD; Medtronic) and HeartMate 3 (Abbott Laboratories), include small, continuous-flow centrifugal pumps with magnetically levitated rotors [21,22]. In addition, the HeartMate 3 can generate pulsatility by periodically changing the pump speed [22,23], although the impact of this 'artificial pulse' on the clinical outcomes is still questionable. These characteristics of third-generation LVADs may provide more benefits and less harm to patients who are waiting for HTPL with the support of these devices. Therefore, updated evidence is needed to evaluate the optimal timing of HTPL in patients with third-generation LVADs. However, only a few studies [17-20] may partly include these patients because the use of HVAD and HeartMate 3 as BTT was approved by the FDA in 2012 and 2017, respectively [24,25]. Moreover, one of the third-generation LVADs, the HVAD, was abandoned in the market in 2021 due to safety issues, and only the HeartMate 3 is currently available.

One study analyzed 2,456 patients identified in the UNOS database from January 2011 to March 2014 [17]. In that study, the authors further divided patients into three groups according to the duration of BTT LVAD: <1 year (n=1,590, 64.7%), 1 to 2 years (n=599, 24.4%), and >2 years (n=267, 10.9%). Among the study patients, 13.1% underwent LVAD using HVAD. Study results showed that a duration of LVAD support over 2 years was a significant factor associated with a higher 30-day mortality and lower 2-year survival rate compared to the other two groups. It should be noted that the same group of authors applied different cutoff values in two separate studies [16,17], and study findings from the UNOS database with similar study periods were different according to the cutoff duration [6,17]. In another study [21], the authors included 2,639 fee-for-service Medicare patients between 2009 and 2014. A substantial proportion of patients enrolled in the previous study described above [17] may also have been enrolled in this study, and a lower proportion of patients may have undergone LVAD using the HVAD compared to the previous study. In this study, the authors divided the LVAD patients according to the duration of BTT as <1 month (n=28), between 1 month and 1 year (n=748), and >1 year (n=409). They demonstrated that patients with BTT LVAD <1 month had worse all-cause mortality than the other two groups (1-year survival rates of 74%, 85%, and 88%, respectively). By analyzing the LVAD duration as a continuous variable, they also suggested that the hazard ratio of mortality was highest at 34 days of support, was significantly over one in only the early period (until 34 days), and decreased to less than one at approximately 2.5 months of support.

In addition to studies evaluating the impact of LVAD duration on posttransplant survival, a study analyzed the risk factors associated with severe primary graft dysfunction (defined as the need for mechanical circulatory support within the first 24 hours after HTPL) [22]. In this study, 480 patients who underwent HTPL between 2009 and 2017 at a single institution were enrolled. Along with other risk factors, more than 1 year of LVAD support was a factor associated with severe primary graft dysfunction after HTPL with a hazard ratio of 2.48. The authors discussed that maladaptive remodeling associated with LVAD support, such as changes in systemic vasculature and worsening of right ventricular dysfunction during support, may increase risks after HTPL. Finally, a very recent study [23] analyzed the impact of the duration of mechanical support on HTPL outcomes. Although this study dealt with all types of mechanical circulatory support, instead of focusing solely on LVADs, the authors showed that overall survival up to 5 years after HTPL was significantly lower in 22 patients with LVAD support <24 days than in 73 patients with LVAD support ≥24 days (Table 1) [6,16,17,21-23].

LIMITATIONS

There are limitations in the current evidence that should be noted. First, all the studies reviewed were retrospectively designed. Therefore, confounding variables could not be completely excluded. The most important limitation is a selection bias regarding early HTPL after LVAD. Patients may have undergone HTPL early after LVAD implantation due to unstable patient conditions, which could negatively affect patient outcomes. Second, as described previously, the majority of the data was from the era of second-generation LVADs. Therefore, there may be limitations in extrapolating the results to the current era of third-generation LVADs.

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CONCLUSIONS

Although there are limitations in previous studies, premature or delayed HTPL after LVAD implantation may affect HTPL outcomes. It may be beneficial to perform HTPL at least 1 month after LVAD implantation to improve survival. In addition, more than 90 days of support with LVAD might be beneficial in terms of functional recovery of severely ill ESHF patients. Finally, prolonged LVAD support over 1 or 2 years may be harmful in terms of the occurrence of primary graft dysfunction and early and late mortality after HTPL.

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Conflict of Interest
No potential conflict of interest relevant to this article was reported.

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REFERENCES

1. Park JJ, Lee CJ, Park SJ, Choi JO, Choi S, Park SM, et al. Heart failure statistics in Korea, 2020: a report from the Korean Society of Heart Failure. Int J Heart Fail 2021;3:224-36.
2. Khush KK, Cherikh WS, Chambers DC, Harhay MO, Hayes D Jr, Hsich E, et al. The International Thoracic Organ Transplant Registry of the International Society for Heart and Lung Transplantation: thirty-sixth adult heart transplantation report - 2019; focus theme: donor and recipient size match. J Heart Lung Transplant 2019;38:1056-66.
3. Frazier OH, Rose EA, Macmanus Q, Burton NA, Lefrak EA, Poirier VL, et al. Multicenter clinical evaluation of the HeartMate 1000 IP left ventricular assist device. Ann Thorac Surg 1992;53:1080-90.
4. Truby LK, Garan AR, Givens RC, Takeda K, Takayama H, Trinh PN, et al. Ventricular assist device utilization in heart transplant candidates: nationwide variability and impact on waitlist outcomes. Circ Heart Fail 2018;11:e004586.
5. Bowen RE, Graetz TJ, Emmert DA, Avidan MS. Statistics of heart failure and mechanical circulatory support in 2020. Ann Transl Med 2020;8:827.
6. Grimm JC, Magruder JT, Crawford TC, Fraser CD 3rd, Plum WG, Sciortino CM, et al. Duration of left ventricular assist device support does not impact survival after US heart transplantation. Ann Thorac Surg 2016;102:1206-12.
7. John R, Pagani FD, Naka Y, Boyle A, Conte JV, Russell SD, et al. Post-cardiac transplant survival after support with a continuous-flow left ventricular assist device: impact of duration of left ventricular assist device support and other variables. J Thorac Cardiovasc Surg 2010;140:174-81.
8. Frazier OH, Rose EA, McCarthy P, Burton NA, Tector A, Levin H, et al. Improved mortality and rehabilitation of transplant candidates treated with a long-term implantable left ventricular assist system. Ann Surg 1995;222:327-36.
9. Frazier OH, Rose EA, Oz MC, Dembitsky W, McCarthy P, Radovancevic B, et al. Left ventricular assist system. Multicenter clinical evaluation of the HeartMate vented electric left ventricular assist system in patients awaiting heart transplantation. J Thorac Cardiovasc Surg 2001;122:1186-95.
10. Kormos RL, Cowger J, Pagani FD, Teuteberg JJ, Goldstein DJ, Jacobs JP, et al. The Society of Thoracic Surgeons Intermacs database annual report: evolving indications, outcomes, and scientific partnerships. J Heart Lung Transplant 2019;38:114-26.
11. Benjamin EJ, Blaha MJ, Chiuve SE, Cushman M, Das SR, Deo R, et al. Heart disease and stroke statistics-2017 update: a report from the American Heart Association. Circulation 2017;135:e146-603.

12. Purohit SN, Cornwell WK 3rd, Pal JD, Lindenfeld J, Ambardekar AV. Living without a pulse: the vascular implications of continuous-flow left ventricular assist devices. Circ Heart Fail 2018;11:e004670.
13. Kranzl M, Stoiber M, Schaefer AK, Riebandt J, Wiedemann D, Marko C, et al. Driveline features as risk factor for infection in left ventricular assist devices: meta-analysis and experimental tests. Front Cardiovasc Med 2021;8:784208.
14. Kilic A, Conte JV, Baumgartner WA, Russell SD, Merlo CA, Shah AS. Does recipient age impact functional outcomes of orthotopic heart transplantation? Ann Thorac Surg 2014;97:1636-42.
15. Kamdar F, John R, Eckman P, Colvin-Adams M, Shumway SJ, Liao K. Postcardiac transplant survival in the current era in patients receiving continuous-flow left ventricular assist devices. J Thorac Cardiovasc Surg 2013;145:575-81.
16. Takeda K, Takayama H, Kalesan B, Uriel N, Colombo PC, Jorde UP, et al. Outcome of cardiac transplantation in patients requiring prolonged continuous-flow left ventricular assist device support. J Heart Lung Transplant 2015;34:89-99.
17. Fukuhara S, Takeda K, Polanco AR, Takayama H, Naka Y. Prolonged continuous-flow left ventricular assist device support and posttransplantation outcomes: a new challenge. J Thorac Cardiovasc Surg 2016;151:872-80.
18. Brown CR, Khurshan F, Chen Z, Groeneveld PW, McCarthy F, Acker M, et al. Optimal timing for heart transplantation in patients bridged with left ventricular assist devices: is timing of the essence? J Thorac Cardiovasc Surg 2019;157:2315-24.
19. Truby LK, Takeda K, Topkara VK, Takayama H, Garan AR, Yuzefpolskaya M, et al. Risk of severe primary graft dysfunction in patients bridged to heart transplantation with continuous-flow left ventricular assist devices. J Heart Lung Transplant 2018;37:1433-42.
20. Yu SH, Chou HW, Wang CH, Tsao CI, Fu HY, Chen KP, et al. Impact of duration of mechanical support on heart transplantation: hasty transplantation may not have a good long-term outcome. Clin Transplant 2022;36:e14746.
21. Wieselthaler GM, Driscoll GO, Jansz P, Khaghani A, Strueber M; HVAD Clinical Investigators. Initial clinical experience with a novel left ventricular assist device with a magnetically levitated rotor in a multi-institutional trial. J Heart Lung Transplant 2010;29:1218-25.
22. Chatterjee A, Feldmann C, Hanke JS, Ricklefs M, Shrestha M, Dogan G, et al. The momentum of HeartMate 3: a novel active magnetically levitated centrifugal left ventricular assist device (LVAD). J Thorac Dis 2018;10(Suppl 15):S1790-3.
23. Bourque K, Dague C, Farrar D, Harms K, Tamez D, Cohn W, et al. In vivo assessment of a rotary left ventricular assist device-induced artificial pulse in the proximal and distal aorta. Artif Organs 2006;30:638-42.
24. Aaronson KD, Slaughter MS, Miller LW, McGee EC, Cotts WG, Acker MA, et al. Use of an intrapericardial, continuous-flow, centrifugal pump in patients awaiting heart transplantation. Circulation 2012;125:3191-200.
25. Stehlik J, Kirklin JK. The long and winding road to an effective left ventricular assist device: the demise of Medtronic's HVAD. Circulation 2021;144:509-11.

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