"Destination Life" in Japan and the United States: A new lifestyle for heart failure patients with left ventricular assist devices

Michael Yamakawa
Biophysics | Johns Hopkins University Class of 2014

Note: I have submitted a review article to *General Thoracic and Cardiovascular Surgery* that contains identical sources and literature as this paper.

Introduction

Congestive heart failure is generally defined as the loss of the heart's ability to pump blood. It is unfortunately among the most common diseases in the United States, affecting almost 5.8 million Americans. Despite advances in pharmacology and medical devices for patients with congestive heart failure, patients often experience further deterioration of their heart, gradually developing a symptom known as "advanced heart failure" or "end stage heart failure" (ESHF). ESHF patients may have extremely poor quality of life, depending on the number of adverse events that require hospitalization and intensive care.

Over the last 40 years, the gold standard treatment for ESHF patients has been cardiac transplantation, a surgical procedure that provides patients with functional hearts from the donor registry. As of 2011, the post-cardiac transplantation survival rate in America is 85% at the first year, and the median life expectancy spans to about 10 years. However, due to the dearth of donors, the availability of hearts is a major constraint factor when choosing transplantation as an option. In 2011, only 2322 heart transplantations were performed in the United States, while the number of waitlisted patients typically exceeds 3000 patients per year. Fortunately, recent developments of left ventricular assist devices (LVADs) have shown great potential to compensate for the lapses between traditional medical therapy and cardiac transplantation.

LVADs are mechanical, circulatory support devices that assist the function of the left ventricle, the part of the heart that provides the initial driving force for blood to travel throughout the body. Although the idea of a mechanical cardiac pump is not a novel one, it has taken decades to reach the point when current devices like LVADs can be implanted into patients to provide reliable assistance for the heart.

Until the recent milestone achieved by HeartMate II, the most commonly implanted device on the market today, the use of VADs as permanent, circulatory support remained relatively rare, despite international efforts directed towards the advancement of its technologies. Instead, cardiac therapies including bridge-to-transplantation (BTT) and bridge-to-candidacy—in which patients are mechanically supported until they can receive a donor— have been common usages of VADs, as heart transplantations generally yielded much higher survival rates. With devices like HeartMate II on the market, however, the need for patients to be bridged to heart transplantation may begin to diminish. Increasingly, destination therapy (DT)—the lifelong support for advanced heart failure (AHF) patients—is becoming a reasonable option to consider. With the recent large-scale successes of destination therapy with the HeartMate II, a new phrase is becoming more popularly used for this mode of therapy to accurately express our entry into a new biomedical era: "destination life."

This paper describes how the left ventricular assist device is becoming a standard biomedical modality and is an increasingly viable option to consider over heart transplantation. These devices have demonstrated great therapeutic success that offers AHF patients a new lifestyle with a good quality of life.

VADs in the United States: The REMATCH trial & HeartMate II destination therapy trial

For decades, the improvement of the quality of life (QOL) of AHF patients via mechanical circulatory support has been one of the major underlying goals of biomedical research. Instigated by the rise in prevalence of cardiovascular disorder throughout the world, efforts have been directed towards innovating support devices that encounter minimal numbers of adverse events to provide a good QOL that AHF patients otherwise have almost no chance of attaining without a new heart.

The Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) was conducted from May 1998 to July 2001 to evaluate the reliability of left ventricular assist devices (LVAD) as mechanical circulatory support for patients who were ineligible for heart transplantation and thus were searching for alternative therapies. Patients were evenly randomized between traditional medical management and LVAD therapy and were closely monitored for signs of physiological improvement. The HeartMate VE—a predecessor of the currently popular HeartMate II—was implanted in the patients in the device group. Kaplan-Meier statistics estimated a one-year survival rate of 52 percent in the LVAD group and 25 percent in the medical-therapy group, and a two-year survival rate of 23 percent and 8 percent, respectively. This demonstrated superiority of VAD performance over traditional medical treatment [1].

Similarly, the HeartMate II destination therapy pivotal clinical trial during which devices were implanted between March 2005 and May 2007 assessed the use of HeartMate II for permanent support in patients ineligible for transplantation. Patients were randomized between HeartMate XVE—an advanced model of HeartMate VE— and HeartMate. Results showed a 2-year survival rate of 58 percent for HeartMate II, significantly surpassing the performance of its pulsatile predecessor (Fig. 1) [2]. This marked a major milestone for developments in mechanical circulatory support and set a benchmark for destination therapy trials. Thoratec Inc., currently a world leader in pump technology, announced in April 2012 that HeartMate II has been implanted in over 10,000 patients all over the world and is becoming a standard therapeutic choice, as patients enjoy an excellent QOL with unimpeded mobility and minimal limitations to physical activities.

VADs in Japan

There have inherently been lags in the introduction of VAD technologies into the Japanese market, largely due to its extreme shortage of donor organs [3]. Until 2009, the Organ Transplant Law

proved to be a large barrier between patients and donor organs by stringently restricting the procurement of organs to those who had familial permission (by which time the organs are typically unviable). Consequently, the waiting period for heart donors exceeded 800 days, urging the government to approve devices that would support patients for this length of time. Although there was a great urgency for a reliable bridge-to-transplantation device to be on the market, contemporary implantable VADs were not available for patients in Japan until 2009.

Bridge-to-transplantation therapy was a commercially available treatment for patients in the United States since 1992 starting with Abiomed 5000 (ABIOMED, Inc., Danvers, MA). On the other hand, the Japanese Ministry of Health, Labor, and Welfare (MHLW) had not approved for the commercialization of a contemporary implantable BTT device until 2009, leaving patients with a small range of options, including the Toyobo VAD, which was designed almost 30 years ago as a pulsatile, paracorporeal device.

The United States then approved the HeartMate VE for destination therapy in 2002 after its dependability as permanent support was demonstrated in the REMATCH trial. On the other hand, clinical trials for BTT approval in Japan with HeartMate VE were finally initiated in 2001, almost 5 years after it was approved for BTT in the United States. Between November 2001 and June 2003, five patients with New York Heart Association (NYHA) class IV end-stage heart failure who were supported with HeartMate VE was evaluated for improvement during the bridging period. All five patients improved to NYHA class I or II, with a one-year survival rate of 100%. This prospective, multicenter trial indicated that the HeartMate VE could effectively bridge patients to heart transplantation in Japan [4].

Between 2009 and 2010, an auspicious period for the improvement of cardiac therapy in Japan, the parliament voted to revise the Organ Transplant Law to increase the number of donor organs in the

registry. Concurrently, the HeartMate XVE (Thoratec), DuraHeart (TerumoHeart, Ann Arbor, MI, USA), and EVAHEART (Sun Medical, Nagano, Japan) LVADs were approved for BTT. The Jarvik 2000 and HeartMate II are currently pending approval [5]. In Japan, the first successful case involving DuraHeart for BTT was reported in 2010, with the bridging period spanning 437 days [6].

DuraHeart is the first, magnetically driven, centrifugal LVAD that eliminates contact between the impeller and the driving mechanism, consequently reducing the likelihood of thrombus and hemolysis. In 2011, it was reported that eight Japanese patients, who were supported by the Toyobo LVAD, switched to DuraHeart bridge to bridge therapy. The apical cuff was not replaced because its size was equivalent to that of DuraHeart, eliminating potential complications that may arise from cuff replacement and reducing operation time. All exchanges were performed safely, but three patients had complications due to infections observed prior to the exchange on the Toyobo VAD cannulation site [7]. This suggests that patients currently supported by Toyobo VAD in Japan may consider the option of switching to DuraHeart- effectively undergoing bridge-to-bridge therapy- to enjoy the advantages of a newer LVAD model.

Cardiac Transplantation—the gold standard treatment of heart failure

Cardiac transplantation has been the gold standard treatment for advanced heart failure patients who are not amenable to other treatments, such as valvular surgery, coronary artery bypass grafting, or LV volume reduction therapy. It has been associated with the greatest survival benefits for patients in all demographics that are eligible for the operation. Unfortunately, there are not enough donors available for every AHF patient, and patients may be ineligible for transplantation if they are over 60 years old, have severe irreversible pulmonary hypertension, or other life-threatening conditions that would severely affect the life expectancy regardless of transplantation. The average waiting period for

a donor in the United States is approximately 6 months, allowing patients to be bridged to transplantation in a rather short period of time with a VAD [8].

There have been multiple studies on the QOL of post-transplant patients in the United States, based on both short-term and long-term data, which date as far back as 1993. In Japan, however, there have been no studies that account for the QOL of these patients. Surveys that compare post-implantable LVAD QOL and post-heart transplant QOL is warranted. They will have important implications for the viability of permanent implantable LVAD support.

Evolution of VAD technology

As exemplified by the REMATCH and HeartMate II DT trials, patients supported by LVADs have had unprecedented survival rates. The use of these devices has increasingly become an attractive choice for AHF patients with contraindications to transplantations that can be gradually remedied. This "bridge-to-candidacy" strategy can eventually allow patients to be put on the transplant list.

Recently, however, prospects of LVADs as a viable alternative to heart transplantation are becoming more realistic, as the miniaturization and increased durability of these devices have rendered them safer and more effective (Fig. 2). Second generation LVADs have distinguished themselves from their predecessors with the rotary blood pump, which allows blood to be channeled with a continuous flow. The compact design supersedes the previously bulky model and eliminates the reservoir chamber and valves (Fig. 3). The lack of a pusher plate or valves also decreases the chance for mechanical failure [9]. HeartMate II is currently the most successful second generation LVAD for BTT and destination therapy and is the only commercially available, continuous flow LVAD in the United States and Europe. While the survival rate between those implanted with second-generation and first-generation devices does not differ significantly after these patients undergo transplantation, the group implanted with second-generation devices experienced lower early rejection rates and infection rates

[10,11]. INTERMACS reported that the number of continuous-flow LVADs that are implanted significantly exceeds that of pulsatile-flow devices, according to data collected between June 2006 and June 2010 (Fig. 4). The third generation LVADs, including DuraHeart, also utilize rotary blood pump technology. Its distinguishing feature, however, is its hemodynamically or magnetically levitated pieces that reduce the friction caused by rotation. DuraHeart was recently approved for BTT in Japan in 2010. Further studies on whether third-generation devices demonstrate significantly improved clinical outcomes than second-generation devices are necessary.

In 2010, the Ev**A**luation of the HeartWare LVA**D** System for the Treatment of A**DVAN**Ced Heart Failur**E** (ADVANCE) evaluated the HeartWare HVAD (HeartWare International, Inc., Framingham, MA)— a third generation, compact device with a non-contacting rotating impeller, for BTT indication in the United States [12]. The HVAD provides flows up to 10L/minute in a relatively small and lightweight device [13], and thanks to these qualities can allow for pericardial placement, limited cardiopulmonary bypass time, a small diameter percutaneous driveline, and elimination of an abdominal pump pocket, beneficial features that have not existed in other models. ADVANCE results suggested similar frequency in adverse events as HeartMate II and indicated a 180-day survival rate that exceeds 90%. Furthermore, ADVANCE's comparison between HVAD performance and the control group from the NIH-sponsored Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) Registry is a novel approach towards clinically investigating the performance of future devices. It may be an approach that can be incorporated into Japanese pivotal trials when data is further collected by the Japanese Registry for Mechanically Assisted Circulatory Support (J-MACS). The HVAD is also undergoing another randomized clinical trial called the Evaluation of the HeartWare Ventricular Assist System for Destination Therapy of Advanced Heart Failure

(ENDURANCE) in the United States, which is investigating the performance of HVAD in comparison to other continuous flow devices for destination therapy [14].

The evolution of devices is also observed during clinical trials. During the REMATCH trial, for example, device modifications, including the addition of parts and release of pressure, increased survival benefits of patients during the enrollment period. In fact, between the first and second year, there was a 15% improvement in survival rate in patients receiving the device who were enrolled in the second half of the trial compared to those who were enrolled in the first half [15]. Thoratec soon replaced HeartMate VE with HeartMate XVE, which had modified features of the former that proved to benefit patients during REMATCH [16]. Further improvements in survival benefits in devices are anticipated as innovative strategies are being improved and device modifications are routinely introduced in practice. While the improvement of the survival rate of post-transplant patients remain difficult to achieve, the constant evolution of LVAD technologies are inevitably going to assist the rise of LVADs as the next gold standard therapy for heart failure.

A new era with LVADs: destination life

As VAD therapy has gradually entered mainstream practice, INTERMACS was established as a joint effort between National Heart, Lung, and Blood Institute (NHLBI), the Centers for Medicare and Medicaid Services (CMS), and the FDA in 2006 to monitor the growth of device utilization. There has been an almost 10-fold increase in the number of VADs used for lifelong support in transplant-ineligible patients [17]. According to INTERMACS data, the percentage of devices implanted for destination therapy increased from 8.4% in 2006 to 13.8% in 2010 (Table 1) [18]. J-MACS is currently being developed to track the progress of device usage in Japan, as well.

VADs have thus been raising therapeutic standards for AHF patients, and will soon reach the survival expectations observed in post-cardiac transplant. With devices like HeartMate II supporting

thousands worldwide, new hope for improving the lives of those diagnosed with advanced heart failure without the worry of waiting for a donor is disseminating. In fact, HeartMate II currently provides support for almost 4500 patients in the United States, a number significantly higher than the number of heart transplants, which was around 2000. The United States has thus entered a generation when the usage of devices surpasses transplantation operation for a greater population of AHF patients.

Unlike medical therapy and implantations of BTT devices that served to improve conditions until an organ was available, the performance of contemporary implantable LVADs are able to offer a new lifestyle for AHF patients who have been restrained from physical activities. A novel phrase, "destination life," appropriately encapsulates this idea. Destination life may become a more common path for advanced heart failure patients in Japan with a slight delay, similar to the lag seen with the introduction of bridge to transplantation. The amount of organ donation in Japan still remains low, and currently the average bridging period still exceeds 2 years, only gradually increasing despite the revision of the Organ Transplant Law. As of December 2010, there had been 89 heart transplantations since 2002, among of which 80 of them were bridged with an LVAD. Of these patients, the average waiting time was 960 days [19]. Furthermore, the survival rate of post-cardiac transplantation patients is very high in Japan, compared to the worldwide averages of 86%, 79%, 72% and 51% (1, 3, 5, and 10-year survival rates, respectively) [20]. The 10-year patient survival rate in Japan was approximately 95% (n=89), far better than the world average [19]. Therefore, while destination life in the United States is an increasingly popular path to consider, bridging therapies may be the primary usage of LVADs for another few years in Japan.

Conclusion

Adaptations in medical practice to the rapid development of LVADs have been demonstrated in the form of a gradual shift of patient selection. With destination life, there have been debates on the

degree of heart failure that should qualify patients for implantation or transplantation candidacy. While the amount of donors in the registry remain relatively low worldwide, the percentage of status II heart failure patients that undergo transplantation remain low as well, as donors are reserved for those who are in worse conditions. This highlights an area of expansion for LVAD usage. In fact, an ongoing pivotal trial, **R**andomized **E**valuation of **V**AD Inter**VE**ntion before **I**notropic **T**herapy (REVIVE-IT) is evaluating the usefulness of LVADs like the HVAD for less sick patients [21].

As LVADs continue to evolve through miniaturization and increased durability, the prospect of minimally invasive LVAD implantations as a means to avoid riskier transplant operations and concomitant complications is becoming a reality. Smaller device models also are more suitable for smaller patients, who may have otherwise not been able to consider implantable VADs due to their small abdominal cavity size. With the dearth of donor organs, we are preparing ourselves to integrate non-biological alternatives for the benefit of advanced heart failure patients who may consider or are required to consider options other than transplantation. Destination life may soon become the gold standard option for a larger population of heart failure patients, of various statuses, in the future.

This work would not have been possible without the contribution of the Franklin Center for Global Policy and Exchange, who funded my project through the William F. Clinger, Jr. Award. I would also like to give special thanks to Dr. Shunei Kyo of Tokyo University Hospital for his mentorship, as well as his guidance and encouragement in my decision to pursue a career in medicine. Finally, I would like to thank Ms. Alicia Haley of Johns Hopkins University for her assistance in connecting me and other university students to the funding that we needed in order to explore a vast range of new and seminal fields and to conduct meaningful research as Hopkins representatives.

References

[1] Rose EA, Gelijns AC, Moskowitz AJ, Heitjan DF, Stevenson LW, Dembitsky W, et al. Long-term use of a left ventricular assist device for end-stage heart failure. N Engl J Med. 2001; 345: 1435-1443.
[2] Slaughter MS, Rogers JG, Milano CA, Russell SD, Conte JV, Feldman D, et al. Advanced Heart Failure Treated with Continuous-Flow Left Ventricular Assist Device. N Engl J Med. 2009; 361: 2241-2251.
[3] Yamane T, Kyo S, Matsuda H, et al. Japanese Guidance for Ventricular Assist Devices/Total Artificial Hearts. Artif Organs. 2010 Sep; 34(9): 699-702.
[4] Omoto R, Kyo S, Nishimura M, Matsuda H, Matsumiya G, Kitamura S, et al. Japanese multicenter clinical evaluation of the HeartMate vented electric left ventricular assist system. J Artif Organs. 2005; 8(1): 34-40.
[5] Kyo S, Minami T, Nushimira T, Ono, M. New era for therapeutic strategy for heart failure: Destination therapy by left ventricular assist device. J Cardiol. 2012 Mar; 59(2): 101-9.
[6] Kurihara C, Ono M, Nishimura T, Saito A, Taketani T, Hisagi M, et al. Use of DuraHeart support for more than 1 year as the first successful bridge to heart transplantation in Japan. J Artif Organs. 2011 Mar; 14(1): 67-9.
[7] Yoshioka D, Sakaguchi T, Saito S, Miyagawa S, Nishi H, Yoshikawa Y, et al. Initial Experience of Conversion of Toyobo Paracorporeal Left Ventricular Assist Device to DuraHeart Left Ventricular Assist Device. Circ J. 2012; 76(2): 372-6.
[8] Stehlik J, Edwards LB, Kucheryavaya AY, Benden C, Christie JD, Dobbels F, et al. The Registry of the International Society for Heart and Lung Transplantation: Twenty- eighth Adult Heart Transplant Report—2011. J Heart Lung Transplant. 2011.
[9] Stewart GC. Givertz MM. Mechanical Circulatory Support for Advanced Heart Failure- Patients and Technology in Evolution. Circulation. 2012 Mar 13; 125(10): 1304-1315.
[10] Ventura PA, Alharethi R, Budge D, Reid BB, Horne BD, Mason NO, et al. Differential impact on post-transplant outcomes between pulsatile- and continuous flow left ventricular assist devices. Clin Transplant. 2011 Jul-Aug; 25(4): E390-5.
[11] Nativi JN, Drakos SG, Kucheryavaya AY, Edwards LB, Selzman CH, Taylor DO, et al. Changing outcomes in patients bridged to heart transplantation with continuous-vs pulsatile-flow ventricular assist devices: an analysis of the registry of the International Society for Heart and Lung Transplantation. J Heart Lung Transplant. 2011 Aug; 30(8): 854-61.
[12] Garbade J, Bittner HB, Barten MJ, Mohr FW, et al. Current Trends in Implantable Left Ventricular Assist Devices. Cardiol Res Pract. 2011; 2011: 290561.
[13] Stevenson LW, Hunt SA. A bridge far enough?. Circulation 2012. [Epub ahead of print].
[14] Milano CA, Simeone AA. Mechanical circulatory support: devices, outcomes, and complications. Heart Fail Rev. 2012 Mar 7.
[15] Park SJ, Tector A, Piccioni W, Raines E, Gelijns A, Moskowitz A, et al. Left ventricular assist devices as destination therapy: a new look at survival. *J Thorac Cardiovasc Surg*. 2005;129:9–17.
[16] Long JW, Kfoury AG, Slaughter MS, Silver M, Milano C, Rogers J, et al. Long-Term Destination Therapy With the HeartMate XVE Left Ventricular Assist Device: Improved Outcomes Since the REMATCH Study. Congest Heart Fail. 2005 May-Jun; 11(3):133-138.
[17] Stewart GC, Stevenson LW. Keeping Left Ventricular Assist Device Acceleration on Track. Circulation. 2011; 123: 1559-1568.
[18] Kirklin JK, Naftel DC, Kormos RL, Stevenson LW, Pagani FD, Miller MA, et al. Third INTERMACS Annual Report-The evolution of destination therapy in the United States. J Heart Lung Transplant. 2011 Feb; 30(2): 115-123.
[19] Egawa H, Tanabe K, Fukushima N, Date H, Sugitani A, Haga H. Current Status of Organ Transplantation in Japan. Am J Transplant. 2012; 12: 523-530.
[20] Ono M. Ventricular Assist device and heart transplantation in Japan. Masui. 2009 Mar; 58(3): 327-36.
[21] Jeevanandam V. Are We Ready to Implant Left Ventricular Assist Devices in “Less Sick” Patients? Semin Thorac Cardiovasc Surg. 2012 Spring; 24(1): 8-10.