Review

New era for therapeutic strategy for heart failure: Destination therapy by left ventricular assist device

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Left ventricular assist device; Destination therapy; Heart transplantation; Bridge to transplant; Heart failure

Summary Until 2010, Japan had been using the Toyobo (Nipro, Osaka, Japan) extracorporeal left ventricular assist device (VAD) developed 30 years ago as a 2–3 year bridge to transplantation (BTT). In contrast, western nations started to use implantable VADs in the 1980s that allow in-home care as destination therapy (DT) as well as BTT. Designated in 2007 as “medical devices in high demand,” the 5 major implantable mechanical hearts are smoothly undergoing clinical testing. The HeartMate XVE (Thoratec Corp., Pleasanton, CA, USA) gained approval from the Ministry of Health in November of 2009, the DuraHeart (TerumoHeart, Ann Arbor, MI, USA) and EVAHEART (Sun Medical, Nagano, Japan) in December 2010, and obtained formal insurance reimbursement in April 2011. The Jarvik 2000 (Jarvik Heart Inc., New York, NY, USA) and HeartMate II (Thoratec) VADs are pending approval. On the other hand, the organ transplantation law allowing explantation of donor organs from brain-dead patients finally passed in July 2009 and was realized in July 2010. This law paved the way to pediatric heart transplants as well as a dramatic increase in overall organ transplantation cases. Because many juvenile patients awaiting donor organs need a VAD as a long-term bridge, development and clinical introduction of pediatric VADs capable of implantation is an exigency. Although expectations for transplants are high, the donor numbers are low. Therefore, the demand for implantable VADs capable of long-term home treatment is extremely high in Japan.

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Introduction

In Japan, the development of ventricular assist devices (VADs) began in the 1960s [1,2], but the preliminary models were only used for post-operative cardiac failure [3]. In those terms, VADs were not used as a “bridge to recovery (BTR),” but as a temporary measure for self-recovery of the heart [4–6]. It was not intended for long-term care for chronic heart failure caused by cardiomyopathy. Recently, the connotation of BTR has significantly changed [7–9], as it now refers to the recovery of the heart through various means of treatment, incorporating surgery [10,11], medicine [12–14], cardiac resynchronization therapy [15–18], apheresis [19], and regenerative medicine [20,17,21], and not just the use of VADs.

On the other end of the spectrum, the artificial heart project that started in the USA during the 1960s aimed to make a replaceable and implantable ventricular device that would be the ultimate alternative to heart transplantation [22]. Because of this prestigious objective, it took nearly 30 years until the completion of AbiCor in 2000 (Abiomed, Danvers, MA, USA) (Fig. 1) [23]. However, in the realm of long-term versatility, it is still far from perfection. Although the term “destination therapy (DT)” insinuates an impeccable alternative to heart transplantation, because of the limits to long-term use at this time, it refers to the care of elderly or unifit patients that are not reasonable candidates for transplant [24]. However, if mechanical heart treatment can surpass the 10-year survival rate for heart transplantation, it is a reasonable vision that VADs will be the most common form of cardiac failure care, excluding the youth [25,26].

Artificial heart treatment in Japan

In Japan, VAD treatment started in 1980 at the Matsui Hospital [3] as a remedy for postcardiotomy heart failure (PCHF) and by November 2009, there has been 1128 cases (Fig. 2) [27]. The majority of those cases are extracorporeal VADs manufactured by the Japanese company, Nipro (Osaka, Japan) (Fig. 3). The first reported case that a VAD was used as a bridge to transplantation (BTT) occurred in 1992 at the Saitama University Medical School and the Osaka University Hospital for a patient with dilated cardiomyopathy [a Nipro left (LV) VAD was used]. The latter case is the first successful BTT, when a 16-year-old male patient went from the University of Osaka to Texas in the USA and endured a 150-day bridge period. After the 1997 establishment of the Organ Transplantation Law, heart transplantation also started, with the first case occurring in 1999 at the University of Osaka. By July 2010 before the revision of the Organ Transplantation Law, there were only 69 heart transplants.

Unfortunately, because the number of donors is severely limited, almost 90% of patients resort to VADs as a BTT and the average bridge period surpasses 800 days. Due to this fact, the use of implantable VADs with minimal complications is imperative. However, only about 20% of VAD patients survive the bridge period, and patients who continue to wait for donors are in virtually the same situation as having received DT, even if the initial purpose was a BTT. A majority of patients with extracorporeal VADs require hospitalization, which still constitutes DT, but with a tremendously low quality of life (QOL). Furthermore, many cardiologists are still uneasy about DT for patients who are not eligible for transplantation [28,29]. On the bright side, the successful implementation of implantable LVADs will allow patients to return home and work, raising the QOL. Branching from this, patients may be able to seek high quality DT as an alternative to transplantation in the near future. Four kinds of implantable LVAD which were submitted with the request document from the relevant academic societies about the highest medical needs, HeartMate XVE (1st generation), EVAD-HEART (2nd generation), DuraHeart (3rd generation), and Jarvik 2000 (2nd generation) in 2007 and one more added, HeartMate II (2nd generation), in 2011. The HeartMate XVE gained approval from the Ministry of Health in November of 2009, the DuraHeart and EVAHEART in December 2010 and obtained formal insurance reimbursement in April 2011. The Jarvik 2000 and HeartMate II VADs are pending approval. We have treated 20 patients with implantable continuous flow LVADs (EVAHEART: 8, DuraHeart: 8, Jarvik 2000: 3, HeartMate II: 1) (Fig. 4) since 2007 in the University of Tokyo Hospital and the clinical outcome of implantable LVADs is quite different from that of paracorporeal Nipro VAD (Fig. 5).

Implantable VAD use in destination therapy

In recent years, many Japanese academic conferences disputed the meaning of DT with the use of implantable LVADs. In 2008, the definition, “long-term home treatment,” was proposed and it has been generally accepted ever since [30]. In the past many total artificial hearts (TAH), such as the 1980 Jarvik 7 [31] and the 2001 AbiCor, underwent clinical trials [32] but none were able to achieve success in DT. Rather in the past 10 years, the use of implantable LVADs in DT for patients not eligible for heart transplants dramatically increased. In the 2001 HeartMate VE REMATCH study (Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure) [33], the results showed that HeartMate VE LVAD treatment excelled over internal therapy. In 2002, the US Food and Drug Administration (FDA) approved the HeartMate VE for DT. Furthermore, in 2005, the HeartMate XVE study showed similar results, which certified increasing DT records (Fig. 6). In the USA, the HeartMate II underwent clinical trials for DT and
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produced considerably enhanced records when compared to the HeartMate XVE. The American Heart Association (AHA) presented these records in 2009 [34]. As a result, the FDA approved the HeartMate II for DT in January 2010.

**The use of destination therapy**

Today’s VAD treatment, like post-operative complications, can generally be broken down into two categories: use in acute cardiac failure, such as acute myocardial infarction or fulminant myocarditis, and use in chronic heart failure, such as dilated or ischemic cardiomyopathy. However, the line of distinction is unclear and is becoming more and more perplexing. That is to say, if a patient is diagnosed with acute cardiac failure and requires a VAD, he or she has three options: (1) Wait for a heart transplant (BTT); (2) Resort to long-term VAD use as a means to DT; and (3) Use with medicinal treatment or cardiac resynchronization therapy (CRT) as means of BTR aiming at recovery of patients’ cardiac function. However, these same options exist for patients with chronic heart failure (Fig. 7). Certainly, in a donor-lacking country like Japan, patients anticipating a BTT may end up receiving DT instead. Likewise, a patient hoping for a BTT may ultimately achieve a BTR by self-rehabilitation. Japan also has a long average wait period for donor hearts, ranging from 2 to 3 years. Therefore, BTT cases require at least a 2-year VAD treatment. In other words, VAD treatment as a BTT in Japan requires as much durability as a DT device used in the USA. Also, because Japan’s current limit heart transplants to the age of 59 years and under, patients who can potentially receive BTT treatment in western countries can only receive DT in Japan. Unfortunately,
the lack of Japanese evidence showing LVAD DT predominance over internal therapy makes it difficult for patients to receive financial reimbursement. In Japan, circulatory internal therapy has many ways of treatment, including CRT-defibrillator, intra-aortic balloon pump, or percutaneous cardiopulmonary support. Because of this, VADs were only used for patients with Stage D cardiac failure (Table 1). It was considered to be a final procedure rather than a routine one. Therefore, the reality is that there is little data that accurately VAD records. However, using a VAD for patients with Stage D cardiac failure makes a bias point on the records because the chances of recovery are slim. Recently in western nations, a bridge to decision (placing a temporary VAD in a patient and waiting for recovery until further action) has become increasingly popular [35,36] due to its financial affordability.

LVAD destination therapy and future prospects

In November 2009, the AHA presented the results of the HeartMate II Destination Therapy Trial. This trial consisted of data contrasting the first-generation pulsatile pump HeartMate XVE (PF VAD) and the second generation, continuous

Figure 3  Nipro left ventricular assist device (LVAD) system. Left: LVAD mounted on anatomical model of the human body. Right: driving console VCT-50.

Figure 4  Four kinds of implantable left ventricular assist device which were submitted with the request document from the relevant academic societies about the highest medical needs, HeartMate XVE (Thoratec Corp.), EVAHEART (Sun Medical), DuraHeart (TerumoHeart), and Jarvik 2000 (Jarvik Heart Inc.).
flow HeartMate II (CF VAD) [34]. The HeartMate II pump was roughly 1/5 the size and 1/3.5 the weight of the HeartMate XVE. It allowed easier implantation for use on smaller patients. Most importantly, this trial showed the HeartMate II’s superiority over the predecessor in terms of 2-year survival rate. The HeartMate II managed a 46% (62/134) survival rate at 24 months, free from disabling stroke or re-operation for device replacement (intention-to-treat) versus an 11% (7/66) rate for the HeartMate XVE. Because the 134 patients with the HeartMate II were all in critical condition, either due to their age, body mass, diabetes, high blood pressure, renal failure, or recent migrant tumors, the 46% survival rate free from major complications was extraordinary. The average age of these patients was 62–63 years old and over

2/3 had ischemic cardiomyopathy with 20% experiencing brain complications. The studies on post-operative complications also showed that many suffered renal failure, pump exchanges, infections, cardiac arrhythmia, and breathing problems (Fig. 8). Perhaps above all, the pump complications 1–2 years after implantation, HeartMate XVE’s largest drawback, dropped sharply (0.06/year vs. 0.51/year), and HeartMate II’s pump exchange rate decreased to 6 cases out of every 100 VADs. In January 2010, the HeartMate II was

![Clinical Outcome of VAD Therapy](image1.png)

**Figure 5** Clinical outcome of left ventricular assist device (VAD) therapy in the University of Tokyo Hospital since 2007. The clinical outcome of implantable continuous flow VADs is quite different from that of paracorporeal Nipro VAD.

![The target of treatment by implantable LVAD](image2.png)

**Figure 7** The target of treatment by implantable left ventricular assist device (LVAD) is to control heart failure at home and regain social activities for a patient who is depending on catecholamine in hospital. The goal of implantable LVAD therapy can be heart transplant (BTT), recovery of the function of native heart (BTR), or life-prolonging treatment (DT, destination therapy). In Japan the heart transplant is restricted extremely, and we should consider it to be second guessing whether the goal is BTT, BTR, or DT. CRT, cardiac resynchronization therapy.

![HeartMate II DT Trial Actuarial Survival](image3.png)

**Figure 6** Survival curve reported in REMATCH study (Heart Mate XVE Destination Therapy Trial) and Heart Mate II Destination Therapy Trial. HeartMate II showed significant higher survival rate at two years over HeartMate XVE [35,36].
Table 1 Inclusion and exclusion criteria for implantable LVAD.

<table>
<thead>
<tr>
<th>Disease and morbidity</th>
<th>Cardiac function</th>
<th>Stage</th>
<th>Medication</th>
<th>Catecholamine and assist circulation</th>
<th>Age</th>
<th>Body surface area</th>
<th>Hemodynamics</th>
<th>Condition</th>
<th>Patient understanding</th>
<th>Exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>End stage heart failure requires heart transplantation including dilative cardiomyopathy, dilative phase of hypertrophic cardiomyopathy, ischemic cardiomyopathy, valvular heart disease, congenital heart disease, and cardiomyopathy following myocarditis.</td>
<td>NYHA: Class III–IV (Past history of Class IV)</td>
<td>Stage D (patient with end-stage disease who is frequently hospitalized for chronic heart failure or who requires special treatments such as LVAD, artificial heart, inotropic infusions, heart transplant or hospice care)</td>
<td>Patient already receiving maximal medical treatment with digoxin, diuretics, angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, nitrates, β-blocker</td>
<td>Depending on dobutamine, dopamine, epinephrine, norepinephrine, phosphodiesterase III inhibitor, or intra-aortic balloon pump, extracorporeal ventricular assist device</td>
<td>Under 65 years is desirable (depending on physical strength, it takes aged 65 and over into consideration)</td>
<td>A system prescribes individually</td>
<td>Stage D, past history of NYHA Class IV</td>
<td>The patient in which high QOL can be obtained by participating in medical treatment, can perform long-term home treatment, and can expect social rehabilitation by the patient to whom the prolongation of life could not be expected under other medical treatment and, to whom the obstacle of the QOL was carried out remarkably</td>
<td>She/he understands the limit and complications of an assisted artificial heart, and an understanding and support of a family are obtained</td>
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<tr>
<td>Inclusion criteria</td>
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<td></td>
<td>Infection</td>
<td>Respiratory ailment</td>
<td>Cardiovascular disease</td>
<td>Neuropathy</td>
<td>Other organ disease</td>
<td>Pregnancy</td>
<td>Others</td>
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<td></td>
<td>Serious infection</td>
<td>Serious chronic obstructive pulmonary disease</td>
<td>Advanced pulmonary hypertension</td>
<td>Pulmonary artery embolism whose symptoms were shown within 30 days</td>
<td>The early stage after open heart surgery (about two weeks)</td>
<td>The abdominal aneurysm and the serious peripheral vascular disease which cannot be treated</td>
<td>Thoracic aortic aneurysm, left ventricular aneurysm, ruptured interventricular septum</td>
<td>Aortic insufficiency more than moderate degree</td>
<td>Calcification critical in the thoracic aorta</td>
<td>Serous damage in the central nervous system</td>
</tr>
</tbody>
</table>

LVAD, left ventricular assist device; NYHA, New York Heart Association; QOL, quality of life.

approved for DT use, and due to this, it is thought that DT will improve drastically.

Complications with LVAD destination therapy and the trend in the USA

Due to the expensive price, VADs in the USA can cost over $150,000 including the surgery fee, the use of LVADs for DT has been strictly controlled. In the early periods of LVADs, the hospital and insurance company had contracts that were in favor of the insurance company. Therefore, hospitals had to be prepared for a fairly large financial loss when they installed LVADs [37,38]. In Japan, Novacor (Rueil-Malmaison, France) was approved by insurance agencies as BTT appropriate in 2004. However, due to the fact that the old model was approved and cost a large sum to exchange batteries, the manufacturer could not maintain use of the
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Figure 8  Comparison of two-year event-free survival rate (free from death, disabling stroke, or re-operation for device replacement) between CF LVAD and PF LVAD. Significant superiority of CF LVAD in two-year event-free survival rate (46% vs. 11%) [36]. CF, continuous flow; LVAD, left ventricular assist device; PF, pulsatile flow.

product and dropped out of the competitive market in 2 years. Japanese academic societies have repeatedly asked for insurance reimbursements for device maintenance past 91 days for implantable LVADs. This time, in regards to the EVAHEART and DuraHeart VADs’ manufacturers’ approval and insurance reimbursements, the academic society’s main concern is that those new regulations do not shape the Japanese market for implantable LVADs [39]. Without a structured market, implantable LVADs will disappear, much like the Novacor VAD. Furthermore, patients waiting for

Figure 9  Changes of insurance reimbursement of the HeartMate left ventricular assist device (LVAD) implantation surgery by Medicare in the USA. Although it was a little less than 40,000-dollar reimbursed in 2002 when destination therapy by Heartmate VE was recognized, insurance reimbursement was increased to almost 200,000 dollars in 2010 when HeartMate II was recognized. (Thoratec data; 2009/2010 Reimbursement Overview: HeartMate II.) CMS, US Centers for Medicare and Medicaid Services.
donor hearts will be forced to have extracorporeal VADs and hospitalization. Hospitals will also suffer because patients who stay for an extended period of time do not increase profits. Extended stays also point to the unsolved problem of hospital room overcapacity. The current revision provides reimbursement for pump device of 18, 100,000 yen, and for over 91 days and a monthly 245,000 yen; however, even with this revision BTT cost for 3 years can be reduced about 49% with CF LVAD from that with Nipro VAD [40]. From now on, many experts anticipate that manufacturers will not experience a deficit and a structured market will soon appear. On the other hand, the implantable VADs for DT (2002) were approved by the US Centers for Medicare and Medicaid Services (CMS) and the annual reimbursement levels increased considerably from $40,000 and under to $196,000 in 2009 (Fig. 9). Especially, the HeartMate II implantation surgery at teaching hospitals received $290,000, which indicates “high quality medical care” for that medical institution. Clinical effectiveness and medical costs should correlate with one another in a capitalistic economy through market theory. By initiating that correlation, the competitive race to manufacture high quality medical devices finally begins [41–43]. Also, this motivation for higher achievement is vital to Japan’s medical device industry.

Conclusion

In Japan, the fact that an extracorporeal VAD developed 30 years ago that gained approval 30-day use and medical reimbursement for acute heart failure in 1994 which was not permitted for BTT use until 2006, being used as a 2–3 year BTT is complete nonsense. Not only does forcing long-term hospitalization during the bridge period significantly reduce patient QOL, but it also limits the hospital’s profit due to the lack of open beds for new patients. Supporting hospitalization for over 20 patients with VADs is an extreme burden on the hospital and two-thirds of them are not able to receive a donor organ. In summary, the lack in quality and quantity of VADs has been solely caused by government administrations. In developed nations such as the USA, patients are allowed to recover at home as a BTT or DT. In contrast, the current regulation in Japan severely limits the number of VAD patients. Is this something that can be overlooked? As Japan attempts to provide everyone with fair medical care, in reality, the administration is restraining patients with 30-year-old VADs in hospitals until they either receive a donor heart or pass away. There is definitely a need to clearly say that something is wrong. The clinical trials for the 5 major implantable LVADs designated in 2007 are going smoothly. The first end point observation (6 months after implantation) has been completed and the HeartMate XVE was approved in November 2009, the Dura-Heart and EVAHEART in December 2010; Jarvik 2000 and the HeartMate II are pending approval. In contrast, the regulations for heart transplants are more than 10 years behind. The new organ transplant law passed in July 2009. There is much anticipation that this new law will carve the way for pediatric organ transplants. Since minors have a high demand for long-term LVADs due to the extended bridge period, new, improved VADs are needed more than they ever were.

References


