1. Introduction

Heart transplantation provides considerable survival benefits for patients with end-stage heart failure, but it is available for only a small fraction of such patients all over the world due to donor shortage. Therefore, many heart transplant candidates require long-term support by a left ventricular assist device (LVAD) while they await transplantation. However, the long-term LVAD support can result in serious complications such as cerebrovascular accident (CVA) and infection, which are the leading cause of death and the primary reason for elimination from transplant eligibility in patients supported by LVAD (Rose EA et al., 2001; Holman WL et al., 2009). In Japan, only less than 100 organ transplants from brain-dead donors have been performed over the past 10 years. The mean waiting period for heart transplant candidates after LVAD surgery frequently exceeds 2 years. In addition, the only available LVAD covered by the National Health Insurance System in Japan is pulsatile extracorporeal LVAD (Toyobo-LVAS®; Nipro, Tokyo, Japan). Implantable LVADs have not yet been approved and are still under clinical trials, awaiting approval by the Ministry of Health, Labour and Welfare as of October 2010.

Toyobo-LVAS® was primarily designed for short-term support, but it is used in Japan over the long term as a ‘bridge-to-transplant’ device (Figure 1). Patients supported by pulsatile extracorporeal LVAD cannot be discharged from the hospital, and cannot leave the intensive care ward without attendant medical doctors. Some patients required to be supported by such device for 4 years until being transplanted.

Given these circumstances, the long-term management skills of Japanese cardiologists for overcoming “extracorporeal pulsatile” LVAD–related complications have improved over time, with the 1-year survival now being 82% (Sasaoka T et al., 2010).

The extracorporeal pulsatile LVAD is the devise that is not utilized in a first line anymore in a world except for Japan. However, CVA and infection, on which we have paid considerable attention during long-term management of extracorporeal pulsatile LVAD, still remain to be important complication even in the era of new generation continuous flow devises. Therefore, we believe that our delicate care for such complication to accomplish long-term survival in patients supported by extracorporeal pulsatile LVAD is worthwhile information even today.

In this chapter, we focused on the management strategies of CVA and infection in patients with extracorporeal pulsatile LVAD according to our past 10 years experience.
2. Survival rate and frequency of complications after extracorporeal pulsatile LVAD

Recently, the survival rate and transplant rate of patients supported by pulsatile extracorporeal LVAD (Toyobo-LVAS®) in Japan have improved considerably. The National Cerebral and Cardiovascular Center (NCVC) (Osaka, Japan) is one of the main heart transplant institutions in Japan, which underwent nearly half of the all heart transplant cases performed in Japan. The technology of Toyobo-LVAS® was initially developed based on the basic research conducted by Takano et al at NCVC in 1982, with collaboration with Toyobo Co., Ltd. in Japan. Accordingly, the NCVC has most experience in Toyobo-LVAS® surgeries and has been mostly familiar with devise management in Japan. Thus, as a representative data of clinical outcome after Toyobo-LVAS® surgery, we introduced the papers regarding Toyobo-LVAS®, which were recently published by our NCVC group (Takahashi A et al., 2010; Sasaoka T et al, 2010).

In order to describe how the survival after Toyobo-LVAS® improved over the years, the retrospectively review of 69 consecutive patients with Toyobo-VAS® as a bridge to heart transplantation between 1994 and 2007 at NCVC were shown. Thirty patients who had LVAD surgery between 1994 and 2000 were assigned to group A, and 39 patients who underwent surgery between 2001 and 2007 were assigned to group B.

2.1 Outcome after extracorporeal pulsatile LVAD surgery over the years

The demographics of patients and the severity of heart failure as indicated by laboratory and hemodynamic examination before LVAD surgeries were not significantly different between the groups. However, the duration of LVAD support was significantly longer in the recent era (group B) than that in the initial era (group A). Mortality was significantly higher in the initial era (group A) than in the recent era (group B). Table 1 and Figure 2 summarizes the outcomes of patients.

Figure 3 shows Kaplan-Meier survival curves of these patients. Survival after LVAD surgery was significantly lower in the initial era (group A) than that in the recent era (group B). Figure 4 shows the causes of death in both groups of patients. The proportion of deaths due to CVA was significantly higher in the initial era (group A) than that in the recent era (group B) (50% vs. 13%, p < 0.0001), whereas that of infection did not differ significantly between two groups. The proportion of deaths due to right ventricular failure, defined as fatal liver or renal insufficiency under LVAD support and requirement of inotropic agents, was higher in the recent era (group B).

2.2 CVA after pulsatile extracorporeal LVAD

Among the 69 patients studied, 37 patients developed CVA after pulsatile extracorporeal LVAD. The incidence and outcome after CVA in the patients are summarized in Table 2. Rapid reversal of warfarin-induced anticoagulation was attempted in all patients who developed intracerebral hemorrhage (Takahashi A et al., 2010). Vitamin K was never used after the events. Prothrombin complex concentrate (PCC), which contains a high level of vitamin K-dependent coagulation factors II, VII, IX and X, rapidly and effectively reverses warfarin-induced anticoagulation. This product (PPSB-HT®; Nihon Pharmaceuticals, Tokyo, Japan) has become available since 2001, and it has been used for emergency reversal of warfarin-induced anticoagulation in cases of intracranial bleeding, intra-abdominal hemorrhage and cardiac tamponade.
Neither the incidence of CVA nor the proportion of CVA that required succeeding neurosurgery differs significantly between two groups. However, the proportion of patients in which CVA led to death was significantly higher in the initial era (group A) than that in the recent era (group B). The proportion of patients treated with PCC after CVA was significantly higher in the recent era (group B) than that in the initial era (group A). Figure 5 shows the Kaplan-Meier survival curves of patients who developed CVA. The survival rates of patients with CVA episodes were significantly lower in the initial era (group A) than that in the recent era (group B).

2.2 Infection after pulsatile extracorporeal LVAD
Among the 69 patients studied, 53 patients developed systemic infection (SI) after pulsatile extracorporeal LVAD. SI was defined as a positive blood culture when patients developed any symptom of infection. Table 3 summarizes the incidence of SI among the patients studied. Neither the incidence of patients who developed SI nor the proportion of SI leading to death differed significantly between two groups. In addition, the cumulative number of SI episodes and the number of SI episodes per year per patient were not significantly different between two groups. However, although SI itself was not a direct cause of death, a subgroup analysis of patients with a history of SI revealed that the proportion of patients who were alive, including those who received transplant and those who remained on LVAD support, was significantly lower in the initial era (group A) than that in the recent era (group B). The proportion of patients with a history of SI who could undergo transplantation was significantly lower in the initial era (group A) than in the recent era (group B). The duration from infection to death in patients with a history of SI after LVAD surgery was significantly shorter in initial era (group A) than that in the recent era (group B) (256.0 ± 203.1 vs. 749.7 ± 328.8 days, p < 0.01).

The proportion of methicillin-susceptible Staphylococcus aureus (MSSA) or/methicillin-resistant Staphylococcus aureus (MRSA) was significantly higher in the recent era (group B) than in the initial era (group A). Linezolid is a powerful synthetic oxazolidinone antibiotic against Gram-positive pathogens that produce toxins (Stevens DL et al., 2007). It is commonly used to combat severe infection with staphylococci including MRSA. Linezolid has been available at our institution since 2001, and has been administered to patients with recurrent refractory MRSA or MSSA infection under all treatment modalities. We decide to use lineszolid under diagnosis of refractory staphylococcal infection.

3. Management of CVA after pulsatile extracorporeal LVAD
In spite of the recent progression of ventricular devises, CVA still remains the leading cause of death and the primary reason for elimination from transplant eligibility in patients supported by LVAD. In addition, transplant recipients with a history of CVA face tremendous difficulties in being reintegrated into society due to neurological after-effects, often for years after transplant.

Patients supported by LVAD require extensive oral anticoagulant therapy. Therefore, rapid reversal of warfarin-induced anticoagulation to prevent hematoma growth and facilitate hematoma evacuation (Hanley JP, 2004) has a decisive impact on prognosis in such patients. The anticoagulation effect of warfarin is related to its ability to inhibit synthesis of the vitamin K-dependent clotting factors II, VII, IX, and X. The appropriate way to reverse the anticoagulation effect of warfarin depends on the clinical situation. Minor or asymptomatic
bleeding needs a less aggressive reversal, whereas serious bleeding requires rapid reversal to avoid succeeding fatal events, regardless of the reason for anticoagulation. For major bleeding, guidelines recommend the administration of vitamin K (5 mg i.v. or oral), and/or PCC (50 U/kg), and/or FFP (15 ml/kg) (British Committee for Standards in Haematology. 1998; Ansell J et al., 2001).

The PCC contains a high level of the vitamin K-dependent coagulation factors II, VII, IX, and X. The PCC promotes a much more rapid reversal of INR than FFP or vitamin K, which is explained by its higher concentration of coagulation factors than FFP. A large volume of FFP is required to achieve adequate INR reversal (Aguilar MI et al., 2007) because vitamin K-dependent coagulation factors vary considerably in FFP, which is not adequate for patients with heart failure. Reversing anticoagulation with vitamin K requires 4 to 24 hours (Aguilar MI et al., 2007) then might cause a fatal situation after CVA events, and also its persistent effect may promote clot formation. Thus, vitamin K administration is not an adequate treatment for patients with CVA as well as any major hemorrhage supported by LVAD, either.

Several studies demonstrated the effect of recombinant activated factor VII on warfarin reversal and reported successful results treating CVH events (Deveras RAE et al., 2002). Although recombinant activated factor VII does reverse the INR, it does not lead to complete reversal of all aspects of warfarin associated coagulopathy. Further studies are required to establish the difference of the effect of warfarin reversal between PCCs and recombinant activated factor VII.

4. Management of Infection after pulsatile extracorporeal LVAD

The REMATCH study showed that sepsis is the leading cause of death (29.5%) after LVAD surgery while cerebrovascular accidents (CVA) are the third cause of death (9.0%) (Rose EA et al, 2001). Coagulase negative staphylococci and staphylococcus aureus have been reported to be the most common pathogens in LVAD–related infections (Malani PN et al., 2002; Nurozler F et al., 2001).

Although a high frequency of side effects has limited its use, linezolid is reported to be superior to vancomycin for treating MRSA infection. In addition, linezolid is a powerful drug to treat severe infections by not only MRSA but also other Gram-positive bacteria, even in peculiar anatomical sites in which therapeutic levels of antibiotics cannot be achieved (Bassetti M et al., 2004). The effectiveness of linezolid for endocarditis due to multidrug-resistant Gram-positive cocci has also been reported. Indeed, most of the patients who had systemic infection described in our observation were infected by Gram-positive pathogens. Therefore, linezolid might be a useful antibiotic agent for treating the most common responsible pathogens in LVAD patients.

Linezolid should be used only in patients with refractory staphylococcal infection. Linezolid-resistant staphylococcus is becoming a recent concern in severe systemic infection, which requires careful observation.

It would be sometimes difficult to identify the causes of infections, which vary depending on the duration after LVAD implantation. In the acute phase, infectious complications may be related to preoperative condition, and/or surgical intervention. In the chronic phase, they are mostly due to infection of exit sites of inflow and/or outflow cannula. Driveline infections may require surgical debridement. LVAD-associated endocarditis and bacteremia may relapse after prolonged courses of antibiotics. Heart transplantation could cure LVAD-related endocarditis by removal of the infected heart; which require careful administration of immunosuppressant under monitoring infection even after transplant.
5. Conclusion

The donor shortage in Japan has been extremely severe compared to other countries. The cardiac donation rate per million population in Japan is only 0.08, whereas it is 7.3 in the United States. The mean duration of LVAD support for transplant candidates was 1220 days. As the duration of support increases, patients are placed at more risk for LVAD-related complications. In addition, only one type of pulsatile extracorporeal LVAD (Toyobo-LVAS®) is available in Japan. This unique situation surrounding LVAD issues in Japan may be quite different from that in Europe or United Stats.

However, under such circumstances Japanese cardiologists have made a considerable effort to accomplish long-term survival of patients supported by such LVAD. Delicate and timely treatment of LVAD-related complications, such as CVA and infection would play an important role in long-term LVAD support. The recent improvement of survival after pulsatile extracorporeal LVAD surgery is associated with prompt warfarin reversal for CVA and well-selected administration of antibiotics for staphylococcus-related systemic infection.

We believe that the LVAD-management strategies described in this chapter could provide worthwhile information even in the era of new generation devises.

6. Tables and figures

Fig. 1. Toyobo-LVAS® system.
Different types of devise console (left upper panel); blood pumps and inflow/outflow cannula (left lower panel); and the chart of LVAD system (right panel). The blood pump was consisted of diaphragm with pulsatile flow through two mechanical valves, operated by pneumatic driven system. The maximum stroke volume was 70 mL per bear under testing with water. Material of blood contacting surface is covered by segmented-polyurethane for medical use.
Fig. 2. Outcome of transplant candidates after LVAD surgery.
The initial era (patients in group A) (left panel) and the recent era (patients in group B) (right panel). (Adopted from Sasaoka T, et al. J Cardiol. 2010; 56:220-8)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group A (n = 30)</th>
<th>Group B (n = 39)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of LVAD support (days)</td>
<td>369.3±337.2</td>
<td>674.6±321.3</td>
<td>0.00029</td>
</tr>
<tr>
<td>Outcome (no. of patients, %)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transplanted in Japan</td>
<td>6 (20.0%)</td>
<td>11 (28.2%)</td>
<td>0.615</td>
</tr>
<tr>
<td>Transferred and transplanted abroad *</td>
<td>2 (6.6%)</td>
<td>4 (10.2%)</td>
<td>0.925</td>
</tr>
<tr>
<td>Died</td>
<td>22 (73.3%)</td>
<td>14 (35.9%)</td>
<td>0.0045</td>
</tr>
<tr>
<td>Remaining on waiting list</td>
<td>0 (0%)</td>
<td>10 (25.6%)</td>
<td>0.0069</td>
</tr>
</tbody>
</table>

Table 1. Outcome after LVAD surgery
* A number of transplant candidates who were transferred and underwent heart transplantation abroad, due to extreme donor shortage and legal constraints in Japan. Japanese organ transplant law did not have criteria for the diagnosis of brain death for those aged under 15 years as of July 2010, thus, pediatric patients had no chance of receiving heart transplant surgery in Japan. (Adopted from Sasaoka T, et al. J Cardiol. 2010; 56:220-8)
Fig. 3. Kaplan-Meier survival curves of patients supported by extracorporeal pulsatile LVAD.
Survival rates of groups A and B at 100 days, 1 and 2 years after LVAD surgery. Solid line and closed squares, group A; dotted line and open squares, group B. (Adopted from Sasaoka T, et al. J Cardiol. 2010; 56:220-8)

Fig. 4. Causes of death after extracorporeal pulsatile LVAD surgery.
The initial era (patients in group A) (left panel) and the recent era (patients in group B) (right panel). (Adopted from Sasaoka T, et al. J Cardiol. 2010; 56:220-8)
Table 2. Incidence of cardiovascular accidents


![Graph showing Kaplan-Meier survival curves](image.png)

Fig. 5. Subgroup analysis of Kaplan-Meier survival curves of patients who developed CVA (group A, n = 17 vs. group B, n = 21) after extracorporeal pulsatile LVAD surgery. Survival rates at 100 days, 1 and 2 years after LVAD surgery, of patients in groups A and B who developed CVA. Solid line and closed squares, patients in group A; dotted line and open squares, patients in group B. (Adopted from Sasaoka T, et al. J Cardiol. 2010; 56:220-8)
### Table 3. Incidence of systemic infection.

SI, systemic infection defined as positive blood culture when patients developed any symptoms of infection. (Adopted from Sasaoka T, et al. J Cardiol. 2010; 56:220-8)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group A (n = 30)</th>
<th>Group B (n = 39)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence of SI (no. of pts, %)</td>
<td>22 (73.3%)</td>
<td>31 (79.5%)</td>
<td>0.754</td>
</tr>
<tr>
<td>Among patients developed SI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proportion of SI leading to death (no. of pts, %)</td>
<td>4/22 (18.2%)</td>
<td>5/31 (16.1%)</td>
<td>0.861</td>
</tr>
<tr>
<td>Proportion of patients presently alive (no. of pts, %)</td>
<td>3/22 (13.6%)</td>
<td>17/31 (54.8%)</td>
<td>0.0058</td>
</tr>
<tr>
<td>Proportion of patients undergoing transplants (no. of pts, %)</td>
<td>3/22 (13.6%)</td>
<td>11/31 (35.5%)</td>
<td>0.049</td>
</tr>
<tr>
<td>Cumulative number of SI episodes (cumulative no. of episodes)</td>
<td>76</td>
<td>102</td>
<td>-</td>
</tr>
<tr>
<td>Number of episodes per year per pts</td>
<td>1.18±0.33</td>
<td>1.26±0.23</td>
<td>0.240</td>
</tr>
</tbody>
</table>

7. References


performance of pulsatile extracorporeal left ventricular assist device. J Cardiol. 2010; 56:220-8


The assist devices will continue adding a large number of years of life to humans globally and empower the medical society to optimize heart failure therapy. While expensive and cumbersome task, the foundation provided in this book reflects a contemporary product of original research from a multitude of different experts in the field. We hope this cumulative international effort provides the necessary tools for both the novice as well as the active practitioner aiming to change the outcome of these complex patients.

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