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EDITORIAL

Towards destination therapy with left ventricular assist devices in Japan

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Medical and electrical therapies for systolic heart failure have improved outcomes and altered the natural history of the disease. Although heart transplantation remains the most successful treatment option for patients with advanced heart failure refractory for these treatment, cardiac transplantation is available for only a minority of patients because of the lack of suitable donor hearts. As a consequence of limited donor availability, left ventricular assist device (LVAD) therapy has become an established treatment for patients with advanced heart failure as either a bridge to transplantation (BTT) or as a permanent alternative to transplantation, i.e., destination therapy (DT).

The Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) trial provided a firm albeit inauspicious proof of concept for the use of blood pumps as an alternative to medical therapy in patients not eligible for transplantation. Small continuous-flow LVADs improved the probability of survival and reduced the risk of device failure compared to larger pulsatile-flow LVADs. Axial-flow LVADs have been the most popular option for mechanical circulatory support. Along with axial-flow blood pumps, some centrifugal blood pumps have also been developed aiming at achieving mechanical circulatory support as well as long-term durability.

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The American Heart Association recommended the use of LVAD implants as DT for patients with advanced heart failure (Class I). As shown in the annual report of the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS), the proportion of patients receiving a durable device as DT increased from 14.7 % in 2006–2007 to 41.6 % in 2011–2013.

In Japan, however, implantable LVADs were introduced in 2009 and have only been applied to heart transplantation candidates; namely for BTT. The use of implantable, nonpulsatile LVADs as DT is not yet authorized, and some patients with end-stage heart failure have undergone extracorporeal pulsatile-flow LVAD (ex-VAD) implantation, especially those whose conditions have critically deteriorated (INTERMACS profile 1). The number of procedures for continuous-flow implantable LVADs (im-VADs) in Japan has been dramatically increasing since their inclusion in the medical reimbursement system. However, the shortage of donors due to social and ethical considerations has been a critical problem for the treatment of severe end-stage heart failure because of social and ethical situations, although heart transplantation under legislation for organ transplantation. Long-term circulatory support extending over 3 years is commonly required for BTT. Thus, in terms of duration of support, a BTT in Japan has become almost equivalent to DT, as is the case in Western countries.

In this issue of *General Thoracic and Cardiovascular Surgery*, Hata et al. [1] published the early and mid-term outcome comparisons between patients with implantable continuous-flow LVADs and those with extracorporeal pulsatile-flow LVAD implantations, both considered the future of DT in Japan. This was a retrospective study, and therefore had inherent limitations. Nevertheless, the study, which was performed at one of the leading heart failure

surgery institutes in the country, shed important light on aspects of mechanical circulatory support treatment meant for DT in the future.

In the past year, some technical improvements and standardization of clinical management have been achieved, as well as changes in the approaches to end-stage heart failure based on data from the INTERMACS database [2]. The INTERMACS was established as a joint effort between the National Heart, Lung, and Blood Institute, the Centers for Medicare and Medicaid Services, and the Food and Drug Administration in 2006 to monitor the growth of device utilization. Evidence-based clinical management of patients equipped with continuous-flow VADs is becoming increasingly important, because the majority of patients were treated with such devices even in non-transplantation centres.

One of the major issues to be addressed in terms of databases and scoring is patient selection for mechanical circulatory support treatment [3, 4]. In recent years, many scoring methods such as INTERMACS have been developed to predict outcomes after VAD implantation; INTERMACS level classification can also predict post heart transplant outcome following LVAD implantation. Patients of INTERMACS levels 1 and 2 have a 5–8 % decrease in 1-year survival compared to other INTERMACS levels. The rates of adverse events will play an important role in driving therapeutic choices for INTERMACS levels 4–7.

The Japanese registry for Mechanically Assisted Circulatory Support (J-MACS) is currently being developed to track the progress of device usage in Japan. As of 2014, over 170 implantable VAD cases using various brands of devices (Duraheart, EVAHEART, HeartMate II, and Jarvik 2000) were already registered, and data obtained from their use had contributed to the better application of LVAD therapy throughout the country [5, 6]. In this particular period when VAD therapy is rapidly growing, J-MACS has already contributed significantly to increasing the introduction of new devices into the country. Because many aspects of VAD therapy may not match Western standards, registration of perioperative and long-term clinical data through J-MACS is critically important for the standardization of Japanese LVAD therapy.

Survival outcomes and severe adverse events

The Japanese BTT study with the continuous-flow LVAD differed from BTT studies in Western countries in a number of aspects, including patient background profiles, duration of support, number of transplants, and availability of other implantable devices. Thus, a direct comparison of the results of this study to the INTERMACS registry data may be unfeasible. Nevertheless, the findings of these studies determined LVAD therapy to be safe and effective for Japanese patients with end-stage heart failure requiring such devices for BTT.

Hata et al. reported that the actuarial survival rates at 1 and 3 years are 92.3 and 79.2 % in the extracorporeal VAD group, and 96.4 and 72.3 % in the implantable VAD group, respectively. There was no significant difference in the survival rates between the two groups. According to the most recent INTERMACS report, actuarial survival was 88 % at 1 year among patients listed as BTT on continuous-flow pumps [3, 4].

The survival outcomes of the above mentioned groups are comparable; patients on extracorporeal VADs (mostly Nipro VAD) had surprisingly good results. Clearly, multidisciplinary approaches and postoperative management play a pivotal role in achieving good outcomes.

The rates of LVAD-related infections (LVADRIs) are high, ranging from 30 to 50 %, primarily because of the presence of a driveline that connects the device to an external battery through an open skin incision [7, 8]. LVADRIs can broadly be classified into driveline infections, pump pocket infections, bloodstream infections, and endocarditis/pump or cannula infections. Diagnostic evaluation and management of these infections can be a major challenge for medical staff involved in the care of these patients. Hata et al. reported that the major cause of readmission in their study was driveline exit-site infection and cerebrovascular events; another Japanese study experienced similar circumstances [5].

Thromboembolic events can occur in up to 20 % of patients who use an LVAD. The aggressive use of anticoagulation agents with newer continuous-flow devices has potentially increased the risk of postoperative bleeding. Some types of infection, especially bacteraemia, are associated with a higher incidence of stroke due to increased endothelial activation and platelet aggregation. Therefore, increased anti-platelet therapy may be warranted during systemic bacterial infections [8]. Hata et al. observed a considerable number of cerebrovascular complications, and approximately 50 % of patients developed some cerebrovascular accidents within 1 year after ex-VAD or im-VAD implantation. The reduction of the thromboembolic events is of paramount importance for those Japanese patients requiring longer durations of support.

Towards DT in Japan

Destination therapy with LVADs has the potential to effectively treat a large number of patients with advanced heart failure who are not eligible for heart transplantation. With the advent of continuous-flow LVADs, safe and effective

long-term circulatory support is available for properly identified candidates. Substantial progress has been made concerning survival and quality of life since DT was first introduced 10 years ago. Advances in patient selection, improved LVAD technology, and optimized treatment strategies provide much optimism for the treatment of a greater number of heart failure patients going forward.

DT with miniaturized rotary blood pumps may become a common option for Japanese heart failure patients in the future as organ donations remain in short supply and LVAD technologies continue to evolve. The success of LVAD provides cardiologists and cardiothoracic surgeons with a new tool for the management of advanced heart failure. Continuous-flow LVADs have emerged as the standard of care for advanced heart failure patients requiring long-term mechanical circulatory support. Evidence-based clinical management of LVAD-supported patients is becoming increasingly important for improving outcomes. Optimizing intraoperative and perioperative care, as well as the monitoring and treatment of other organ system dysfunctions as it relates to LVAD support, are being standardized. A multidisciplinary heart failure team must be organized and charged with providing comprehensive care from initial referral until support is terminated [9, 10].

Medical and socioeconomical indications of DT, however, should be widely discussed before DT is fully adopted in Japan because the state of the economy may hinder its availability to all patients who need it. It is also worth noting that clinical results of Japanese BTT studies are not applicable to future DT results. Transplant-ineligible patients are very likely to be older and much sicker than transplant candidates having multiple comorbidities; thus, future Japanese DT outcomes could be much worse than anticipated. To identify proper candidates for DT, a risk stratification system such as the Destination Therapy Risk Score proposed in the United States can be useful.

In order to establish an appropriate DT system in Japan, communication between the relevant academic, regulatory, and device-manufacturing institutions encompassing all the issues regarding the DT system has to continue. As Hata et al. concluded, documenting clinical outcomes of implantable LVAD therapies in accordance with J-MACS is a critical first step for compiling data from Japanese patients.

In Japan, DT may soon become the gold standard option for a larger population of heart failure patients. Continuous research in the field of mechanical circulatory support will contribute the further development of technologies that are more user-friendly and have less adverse events.

Compliance with ethical standards

Conflict of interest The author declares that there are no conflicts of interest.

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