Mechanical circulatory support devices (MCSD) in Japan: current status and future directions

Abstract The current status and future directions of mechanical circulatory support devices (MCSDs) in Japan are reviewed. Currently used clinical MCSDs, both domestic and imported systems and continuous flow devices that are coming into the clinical arena are emphasized. Clinical MCSDs include the extracorporeal pulsatile Toyobo and Zeon systems and the implantable Novacor and HeartMate I VE. A thorough review is presented of single-ventricle continuous flow MCSDs such as the Terumo DuraHeart and the SunMedical EVAHEART and the biventricular Miwatec/Baylor systems that are on the horizon. The future directions in management of end-stage cardiac patients with MCSDs are discussed, focusing on (1) device selection – pulsatile versus continuous flow devices; (2) single-ventricle support, biventricular support, or replacement; (3) bridge to transplantation, destination therapy, or bridge to recovery; and (4) government regulatory processes and the medical industry. We hope to promote the quality of life (QOL) of end-stage cardiac patients as well as the medical industry in Japan.

Keywords Mechanical circulatory support device (MCSD) · Ventricular assist device (VAD) · Biventricular bypass device (BVAD) · Replacement device · Total artificial heart (TAH)

Introduction Since 1999, heart transplantation has been reinstituted in Japan to support end-stage cardiac patients. To date, 21 patients have undergone heart transplantation, of which 15 (71.4%) were being bridged with a mechanical circulatory support device (MCSD). Approximately 80 patients are currently wait-listed for heart transplantation; around 25 patients per year are added to the list. Of the patients undergoing heart transplantation, the mean waiting time was 502 days as a result of the severe donor heart shortage. The multicenter clinical evaluation of the HeartMate I VE conducted in Japan from 2001 through 2003 revealed that of the six patients enrolled in the study, none had undergone transplantation and all had been on support with a mean duration of 478 days (as of June 2003). The long support duration by MCSD in Japan is similar to that of the REMATCH trial in which destination therapy demonstrated superior 2-year survival over conventional therapy. Destination therapy and/or tandem therapy, with an MCSD in combination with cell transplantation, genetic treatment, and drug therapy, may be an alternative option to circumvent the shortage of donor hearts in Japan. To achieve this goal, we need compact, durable, safe and reliable implantable MCSDs.

Of the 15 patients who had been bridged to transplantation with use of MCSDs in Japan, 10 were using the Toyobo extracorporeal pneumatic device and 5 were using implant-
able devices [two NOVACOR and three HeartMate I (two pneumatic and one electrical)]. The Toyobo patients remained in the hospital because of the danger of infection through the wound site where the inflow and outflow canulas penetrated the skin. The Novacor and HeartMate I patients, however, had been discharged while waiting for a heart transplantation. The quality of life for the patients with extracorporeal devices was questionable in comparison to the patients with implantable devices. In Japan, the 30 years after 1968 without heart transplantation being performed held back progress in MCSD technology; this explains why Japan has had to rely on imported MCSDs. The US-made devices, however, are too large for Japanese patients because the devices require a body surface area (BSA) greater than 1.5 m$^2$. In addition, the price is extremely high (US$140000/device).

The development of a compact, low-cost implantable clinical MCSD has been pushed forward since 1995 as a national project in Japan. Concentrated efforts over the past 10 years are now bearing fruit. As reported at the Rotary Blood Pump Symposium held on August 27, 2004, in Tokyo, we are now witnessing a new era of clinical trials of rotary blood pumps. This paper reviews the current status and future directions of the MCSD in Japan, focusing on continuous flow devices.

**Historical perspective of MCSD progress in Japan**

Although artificial heart research in Japan dates back to the early 1960s,$^5$ it did not move into clinical application until the early 1980s. During the late 1980s, extracorporeal pneumatic MCSDs, both the Toyobo and Zeon/Aisin systems, went through the government approval process as a post-cardiotomy temporary support system.$^6\text{-}^7$ The premarket approval (PMA) was granted in 1990, with reimbursement approval granted in 1994. Because of the long approval process during insurance coverage from 1990 to 1994 and the extremely high cost involved in commercialization of such devices, the momentum gained for using MCSDs slowed down, discouraging further industrial involvement in device development.

As for treatment of cardiomyopathy, in the early 1990s, end-stage cardiac patients did not have any other choice except implantation of an extracorporeal device and then going abroad for heart transplantation. Figure 1 shows a dilated cardiomyopathy (DCM) patient implanted with the Toyobo MCSD and transported in a private jet to the USA in 1992. The patient successfully underwent transplantation after 119 days. Following this successful transplantation, more than ten patients went abroad with the Toyobo device for heart transplantation. This trend continued even after legalization of heart transplantation in Japan in 1997 because of a severe donor heart shortage. In 1996 another patient, this time with a Novacor MCSD, was discharged for the first time in Japan and later successfully underwent transplantation in the USA.$^8$ These sequential events were connected to several national MCSD projects that had started in 1995.

From design, in vitro performance testing, in vivo animal study, to clinical study, a wide range of devices, including pulsatile and continuous flow devices and single and biventricular assist and replacement (total artificial heart, TAH) devices, are under development at Universities, hospitals, national research institutes, and companies. Among them, the Terumo magnetically levitated pump, the Kyocera/Baylor (later to become the Miwatec/Baylor) pivot bearing pump, and the Asin/National Cardiovascular Center (NCVC) electrohydraulic total artificial heart project,$^9\text{-}^{11}$ made up the NEDO (New Energy and Industrial Technology Development Organization) projects from 1995 to 2004. Another national project was the SunMedical Inc. EVAHEART, supported by the Japan Science and Technology Agency (JST).$^{12}$ The University of Tokyo group obtained a grant from the Ministry of Health, Welfare, and Labor to develop an undulating ventricular assist device.$^{13}\text{-}^{14}$ The development of electromechanical MCSDs, both assist and replacement types, is also under investigation at Tokyo Medical and Dental University.$^{15}\text{-}^{16}$ Figure 2 shows a map of MCSD development sites in Japan. In the following section, clinical MCSDs (both pulsatile and con-