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REVIEW

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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.

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

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Introduction

Since 1999, heart transplantation has been reinstituted in Japan to support end-stage cardiac patients.[1] 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.[2] Of the patients undergoing heart transplantion, 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 transplantion and all had been on support with a mean duration of 478 days (as of June 2003).[3] The long support duration by MCSD in Japan is similar to that of the REMATCH trial[4] 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-

Fig. 1. A dilated cardiomyopathy (DCM) patient with a Toyobo mechanical circulatory support device (MCSD) (*left*) and in a jet during transportation from Japan to the USA (*right*)

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 cannulas 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$140 000/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.[6–7] 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 implantion 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 transplantion 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 Aisin/National Cardiovascular Center (NCVC) electrohydraulic total artificial heart project[9–11] 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.[13–14] The development of electromechanical MCSDs, both assist and replacement types, is also under investigation at Tokyo Medical and Dental University.[15–16] Figure 2 shows a map of MCSD development sites in Japan. In the following section, clinical MCSDs (both pulsatile and con-

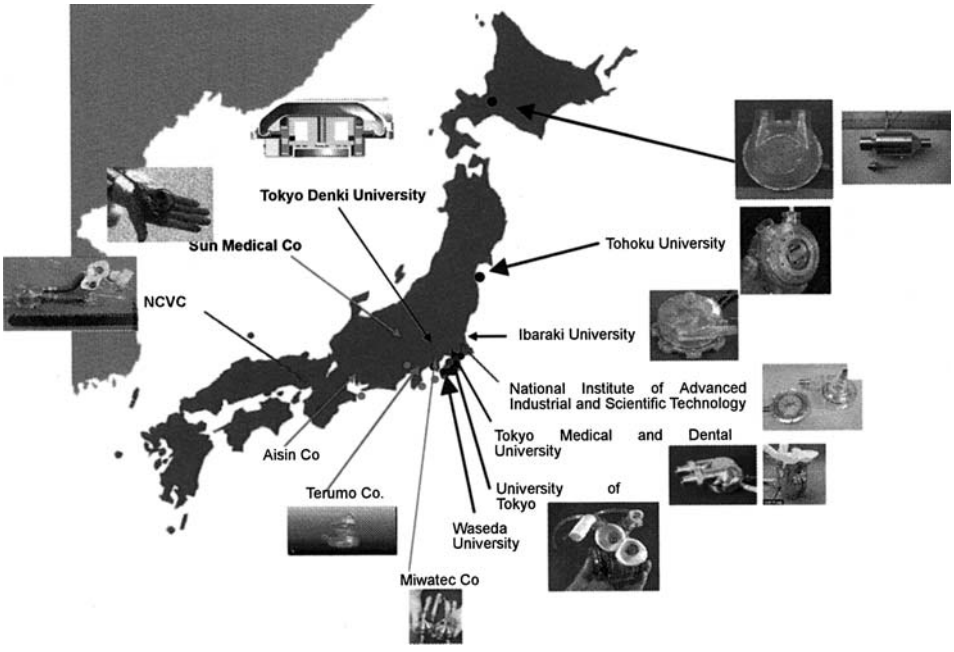


Fig. 2. A map of MCSD development sites in Japan

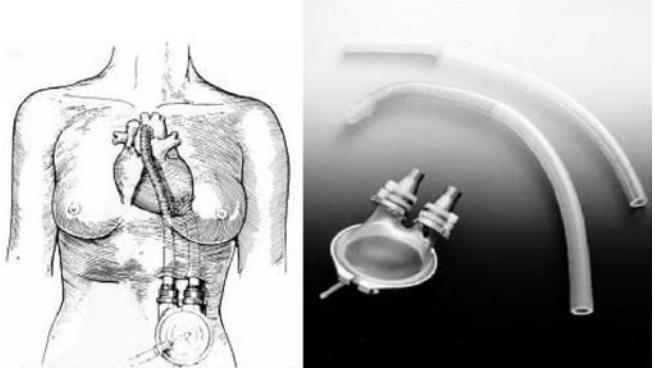


Fig. 3. Toyobo pneumatic pulsatile MCSD. Anatomical configuration of the device (*left*) and pump and cannula system (*right*)

tinuous flow devices, with emphasis on the continuous flow devices) that are now emerging into the clinical arena will be discussed.

Clinical use of MCSDs in Japan

Pulsatile MCSDs

Currently available clinical MCSDs include the Toyobo/NCVC and Zeon/Aisin extracorporeal pneumatic pulsatile blood pumps and the Novacor and HeartMate I VE implantable systems. The Toyobo and Zeon/Aisin systems have been used in approximately 570 postcardiotomy and cardiomyopathy patients. Currently, the Toyobo MCSD has been implanted in over 20 patients at seven centers across Japan (NCVC, Osaka University, Kyushu University, Saitama Medical College, University of Tokyo, Tokyo Women's Medical University, and Tohoku University) that have been set up to carry out heart transplantations.

Figure 3 shows the anatomical placement as well as the inflow and outflow cannulas of the Toyobo MCSD. The blood pump is of the hemispherical diaphragm type, having a stroke volume of 70 cm^3, and is pneumatically operated with a blood-contacting surface fabricated using segmented polyurethane.[17–18] The pump drains the blood from the left ventricular apex and returns it to the ascending aorta. The pump is placed outside the body and is tethered to the external pneumatic control–drive console. The Zeon/Aisin system is also an extracorporeal pneumatic MCSD with a sac type blood chamber having a stroke volume of 40 cm^3. The postcardiotomy clinical evaluation of both devices was reported in 1996 by Takano et al.[19] Other pneumatic pulsatile devices such as the Thoratec and the Thomas Heart were also used in a few patients for temporary support after open-heart surgery in the late 1980s to early 1990s.[19]

The Novacor and HeartMate I VE (Figs. 4, 5) are both imported from the USA and have gone through clinical evaluation in Japan. The Novacor MCSD, imported through Edwards Life Science, Inc., completed its clinical evaluation from 1995 through 1999, obtaining government approval in 2001. Reimbursement approval was granted in 2003 (US$140 000). The HeartMate I, imported through Nipro Inc., completed the clinical evaluation process in 2003 and awaits government approval. Although both devices are implantable and have shown excellent performance in the USA and Europe as bridge to transplantation (BTT) and/or destination therapy (DT) devices,[20–23] their size, price, and the regulatory process are the major limiting factors that have hindered their smooth and wide clinical use in Japan. They are somewhat large for average Japanese patients, particularly for women and children, and require a

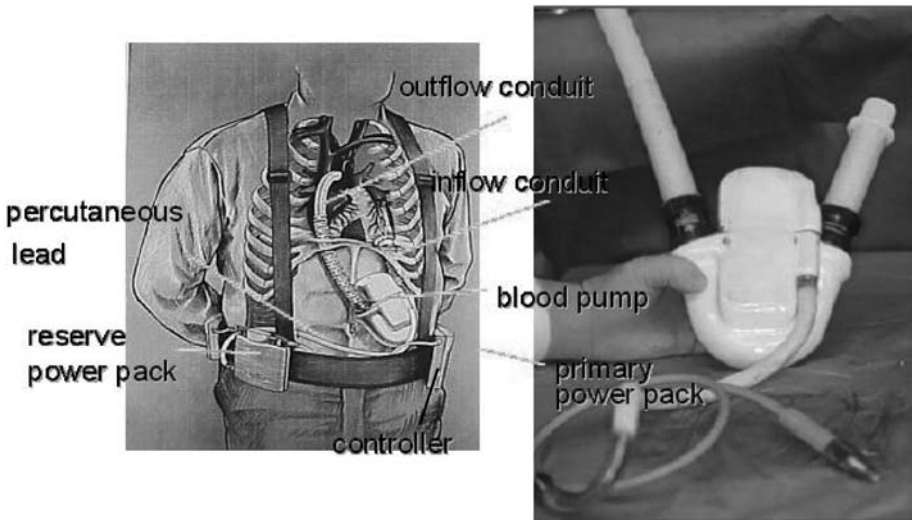


Fig. 4. Novacor implantable MCSD system. Anatomical configuration of the implantable components (*left*) and pumping unit (*right*)

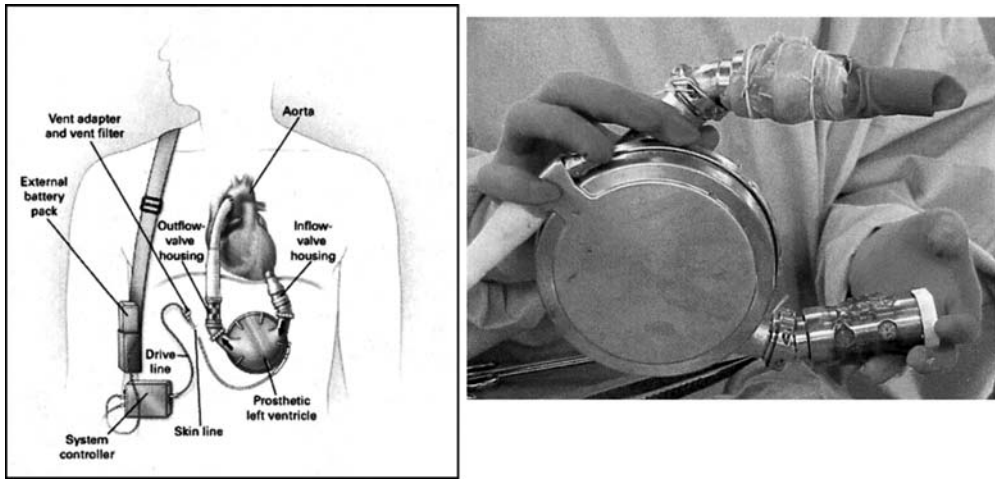


Fig. 5. HeartMate I VE implantable MCSD. Anatomical configuration of the implantable components (*left*) and pumping unit (*right*)

body surface area of over 1.5 m^2. The development of more compact, smaller, implantable MCSDs will promote treatment of end-stage cardiac patients who have been waitlisted for heart transplantation in Japan as well as those in the wider Asian Pacific area.

Continuous flow MCSDs

Continuous flow devices offer advantages over pulsatile devices in terms of (1) compactness and light weight, (2) simple design with a single moving part, (3) no valves being required, (4) no compliance chamber being required for implantation, (4) high efficiency, (5) longer pump life, and (6) the low risk of thromboembolism and infection. However, the physiological consequences and clinical acceptability of continuous or reduced pulsatile flow is under discussion and the answer awaits clinical outcomes.

The two most advanced devices, the Terumo DuraHeart and the SunMedical EVAHEART, are of the centrifugal type, the former having a magnetic levitation (maglev) mechanism to float an impeller without mechanical contact,[9] whereas the latter has a purge mechanism to cool the seal area that supports a rotating impeller shaft.[12] Both devices are extremely compact, small, and have a BSA requirement of around 1.1 m^2. The third continuous flow system is the Miwatec/Baylor biventricular system.[10] Several axial flow devices, from contact bearing to maglev types, are also under investigation in Japan,[24,25] but they are still at the early design and experimental stages. In the following section, the current status of the continuous flow devices that have gone into clinical trials, the DuraHeart and the EVAHEART, and the Miwatec/Baylor system that is close to clinical application, is reviewed.

The DuraHeart

Figure 6 shows the DuraHeart,[26–32] which has a displacement volume of 180 cm^3 and a weight of 540 g. The external diameter is 72 mm and the height is 45 mm. The impeller is

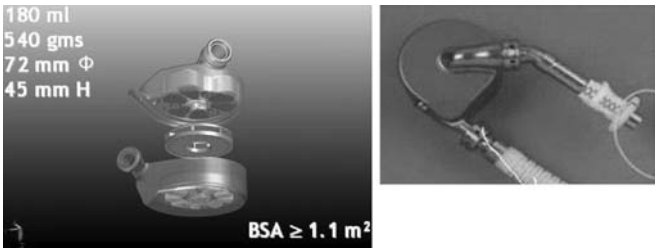


Fig. 6. Terumo DuraHeart MCSD. Top and bottom housings, and impeller (*left*) and pumping unit with inflow and outflow cannula systems (*right*)

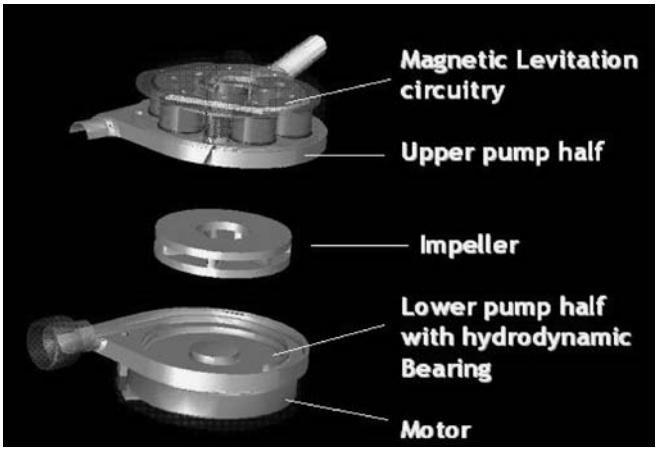


Fig. 7. Exploded view of the DuraHeart

magnetically levitated by the circuit mounted in the upper pump housing, whereas it is driven through an axially coupled magnetic driver in the bottom housing (Fig. 7). A hydrodynamic bearing is also incorporated into the lower pump housing as a safety mechanism in case the magnetic bearing fails. Figure 8 shows a set of curved apical cannulas made of titanium. The external components consist of a wearable controller and battery unit that weighs 1.9 kg altogether. The pump speed can be controlled from 1200 to 2600 rpm and can deliver a flow of 2–10 l/min. The built-in flow estimator based on the motor current provides a sensorless continuous indication of pump flow. Figure 9 shows a console that allows monitoring of the system and adjustment of pump parameters. It can provide patient and system data and can display the stored pump data.

The early engineering model of the DuraHeart developed from 1995 to 1999 had run for a maximum duration of 864 days when implanted paracorporeally in sheep (Fig. 10). In 1999, Terumo moved to the USA to continue with the clinical evaluation of this maglev centrifugal blood pump. From 1999 to 2001, a chronic animal study was carried out in six sheep (who survived for periods of 90–340 days) in Oxford, England. From 2001 to 2002, the system underwent a critical bench testing to evaluate (1) the reliability of critical components, (2) system safety, (3) hydraulic performance, (4) hemolytic performance, and (5) impeller stability. Then, preclinical testing was initiated at a Utah artificial heart laboratory where good laboratory practice had been

Fig. 8. Inflow conduits of the DuraHeart

Fig. 9. DuraHeart console

established. Eight chronic experiments were all terminated electively after 30, 60 or 90 days to confirm hemocompatibility. Reliability testing was conducted from 2003 with the pump being immersed in saline at 37°C. The reliability study confirmed (1) no premature system and/or component failures as a result of design or manufacturing flaws, (2) no latent component failures, and (3) no wear failures in any components.

Clinical trials with the DuraHeart started in January 2004 in Europe. The primary objective of the study is to evaluate the safety and performance of the DuraHeart in

candidates with end-stage left ventricular (LV) failure (NYHA Class IV) who are at imminent risk of death and who are receiving, but not responsive to, conventional therapy. The secondary objectives include (1) to evaluate the safety of the DuraHeart throughout the follow-up period, (2) to evaluate the improvement of the patient's functional status while being supported by the DuraHeart, and (3) to evaluate the DuraHeart system function. The inclusion criteria are (1) referred for and eligible for cardiac transplantation, (2) BSA of greater than 1.1 m^2, (3) NYHA functional class of IV, (4) receiving optimal medical treatment including inotropes, intra-aortic balloon pump (IABP), or both, (5) cardiac index less than 2.2 l/min/m^2 with either systolic blood pressure less than 80 mmHg or left atrial pressure (LAP) or pulmonary arterial diastolic (PAD) greater than 18 mmHg, (6) patient signed informed consent, and (7) all lab and physiological data used for patient evaluation indicates status within 48 h of enrollment. The exclusion criteria are (1) fixed pulmonary hypertension with a pulmonary vascular resistance (PVR) greater than six Wood units, (2) severe chronic obstructive pulmonary disease (COPD), (3) presence of active systemic infection, (4) having a symptomatic cerebrovascular disease, (5) serum creatinine level higher than 5 mg/dl or blood urea nitrogen (BUN) level greater than 100 mg/dl or requiring hemodialysis, and (6) liver enzymes greater than three times the normal upper limit or a total bilirubin level greater than 5 mg/dl.

The status of clinical trials as of August 27, 2004, were as follows: (1) five investigational sites had been selected in Europe, (2) 16 patients had been screened, (3) of the 16 patients screened, 10 patients had been implanted, (4) patient ages were between 29 and 72 with a mean age of 56.4 with BSA ranging from 1.42 to 2.03 m^2 and (5) male to female ratio was 7:3. The clinical results as of August 27, 2004, include: (1) three patients met the primary end-point, (2) there were no device-related cardiovascular accidents (CVA), deaths or infections, (3) four patients were discharged; one patient underwent transplantation after 138 days on the device, and the longest support was 170 days.

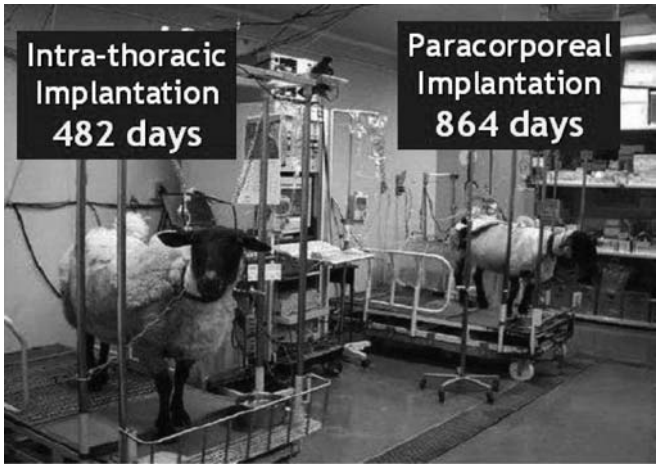


Fig. 10. Early model of DuraHeart implanted in an animal for 482 days intrathoracic and for 864 days (paracorporeal)

The EVAHEART

Figure 11 shows the EVAHEART system,[33–36] which consists of an implantable centrifugal blood pump unit and an extracorporeal fluid recirculating system. The EVAHEART was designed to attain (1) long-term system reliability, (2) freedom from thromboembolic complications, and (3) freedom from systemic as well as local infection. The blood pump is a magnetically driven centrifugal blood pump and has the following features: (1) a valveless continuous flow pump,(2) a simple structure with a single moving part, and (3) construction using titanium and ceramic, which do not deteriorate in the biological environment over a prolonged duration.

A journal bearing supports the rotation of the impeller with recirculating purge fluid lubricating and cooling the bearing area. A small amount of the recirculating saline will enter the blood stream to cool and to prevent thrombus

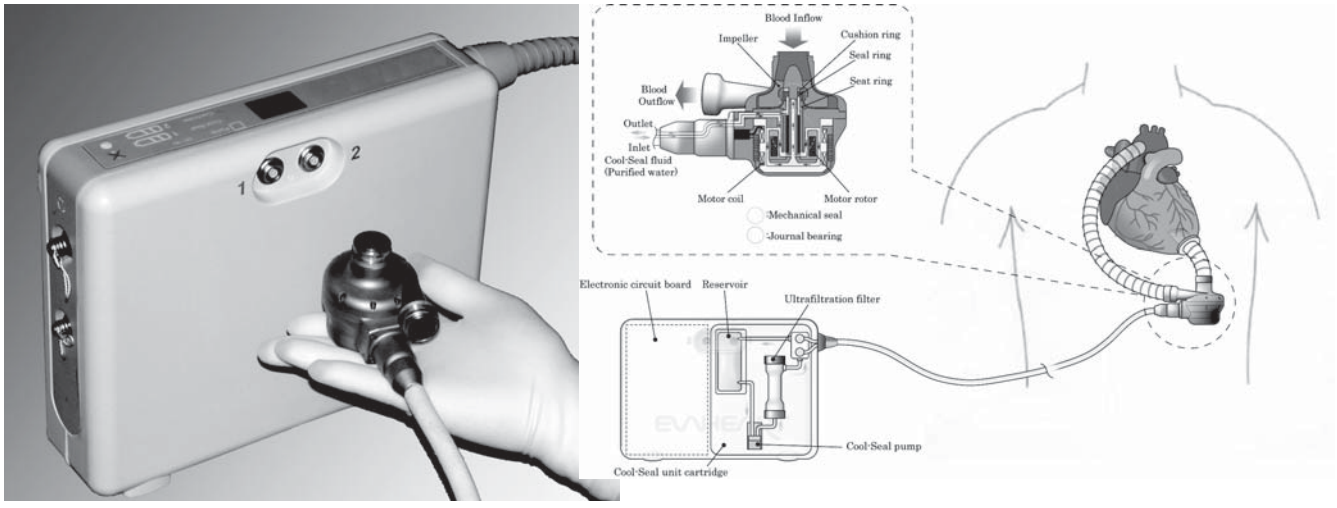


Fig. 11. EVAHEART centrifugal MCSD system (*left*) and implantation scheme (*right*)

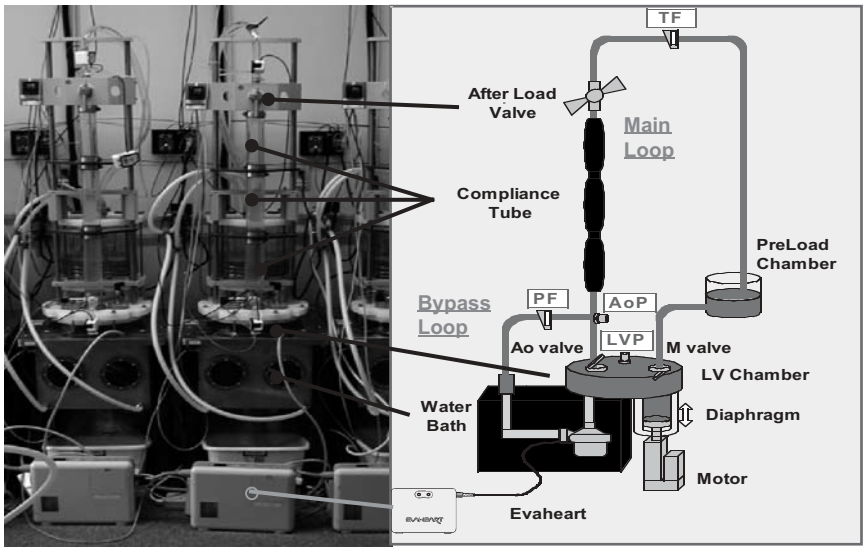


Fig. 12. In vitro system reliability test setup. *PF*, pump flow; *AoP*, aortic pressure; *LV*, left ventricular

formation around the journal bearing area. The journal bearing and the mechanical seal are the only contact points in the blood pump, and it can run semipermanently because of little wear.

System safety and reliability features. The control electronics as well as the sensors are all contained in the control unit outside the body to improve reliability of the implanted blood pump. The system has cleared the UL2601-1 as well as the IEC60601 mechanical and electrical safety requirements. It has a redundant Li-ion battery system to allow 11 h of continuous operation. It can run from an AC adaptor as well as a car battery adaptor. The system also has the capability of storing and recalling the alarm history of all the units.

The EVAHEART was the first in the world to employ a pulsatile mock circulatory system that simulated the internal environment of the biological system. Figure 12 shows the system diagram and the actual setup. Eighteen units ran for 1 year without failure in any system. In particular, pump function and the journal bearings remained without problem. The system's reliability at 1 year was estimated to be about 85%. Concerning the reliability of the mechanical seal, SunMedical has tested 12 units for 6 months. Of the 12 units, 6 were operated at 1800 rpm and the other 6 units at 3600 rpm. If there were no problems, the study duration was extended to 2 years. The wear rate in the mechanical bearing was 21 μm per 6 months, indicating the life of the seal to be over 25 years.

The following mechanical safety tests were also conducted and proved satisfactory: (1) vascular graft mechanical strength test, (2) pump cable mechanical strength test, (3) cool-seal line seal test, (4) pump unit seal test, (5) controller feed-through line connection test, (6) vibration test (JIS C0040), (7) environmental test (high/low temperatures of 45° and −5°C), (8) impact force test (JIS C0041), (9) system transport test, and (10) hemolysis test [normalized index of hemolysis (NIH) less than 0.005 g/100 l].

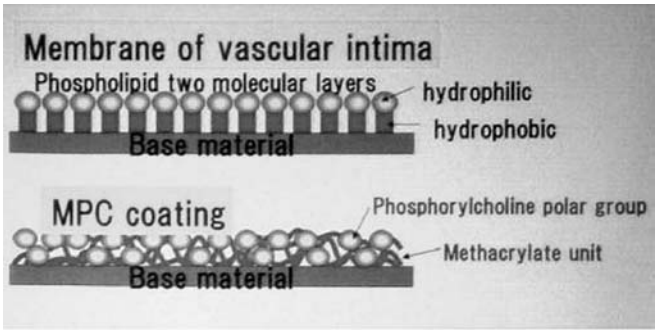


Fig. 13. MPC coating mimicking the membrane of the vascular intima

Antithrombogenic features. The EVAHEART's open vane structure does not generate a stagnant flow area by always maintaining a high blood flow velocity inside the pump head. The pump housing is made of biocompatible stable titanium with the blood-contacting surface coated with a 2-methacryloyloxyethyl phosphorylcholine (MPC) polymer for prevention of thromboembolic complications (Fig. 13). MPC has a bilayer lipid structure that mimics the intimal lining of the vasculature and can provide an excellent blood-compatible surface. The blood is drained from the apex of the left ventricle with a flexible conduit having a zero-gap connector and is returned to the ascending aorta using a polytetrafluoroethylene (PTFE) graft. The animal study was carried out in the USA at the University of Pittsburg and Louisville in a total of 60 animals. The maximum implant duration was 222 days. The experiment was carried out with or without an anticoagulant because of the excellent antithrombogenic properties of the MPC coating. A specially designed zero-gap inflow connector together with MPC polymer coating were key in attaining thrombus-free operation for up to 222 days. Figure 14 shows the autopsy findings of the conventional and zero-gap connectors where thrombus formation was minimized with a zero gap between the tubing and pump port.

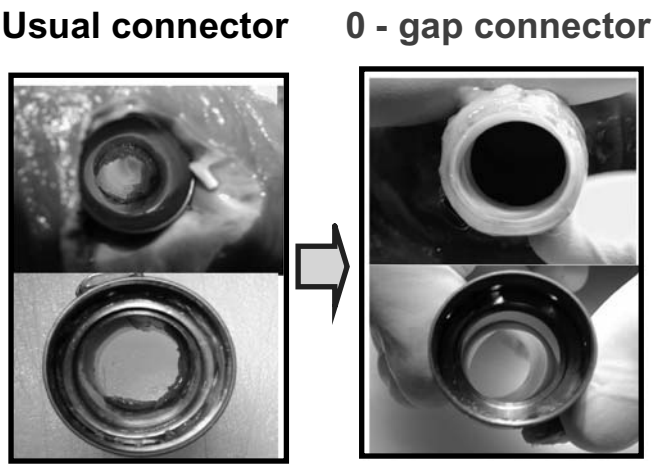


Fig. 14. Comparison of blood compatibility between the conventional (*left*) and zero-gap connector (gap between the port and pump housing is minimized by precision machining) (*right*)

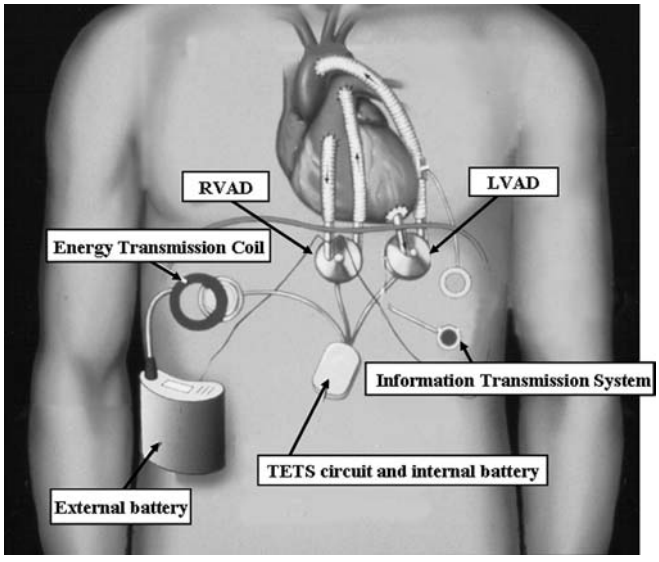


Fig. 15. Overall system concept of the Miwatec/Baylor biventricular MCSD. *RVAD*/*LVAD*, right/left ventricular assist device; *TETS*, transcutaneous energy transmission system

Antisepsis and infection features. The features that prevent systemic as well as local infection in the EVAHEART include: (1) the blood chamber is extremely small, (2) the blood flow is kept high, (3) heat generation is low, (4) mechanical vibration is minimal, and (5) thrombus formation is controlled by the MPC polymer coating. In addition, local infection through the tissue–material interface where the cable penetrates the skin is controlled using a tissue engineering approach. Slow-release basic fibroblast growth factor (bFGF) and a chitosan coating were applied to the cable material to enhance tissue growth and to secure strong adhesion between the tissue and cable. In addition, a special cable holder was designed to suppress movement of the cable around the skin exit area and to reduce the stress applied to the tissue–material interface. Also, the skin-penetration area was kept in a sterile condition. The outer strap was designed to spread the force applied by the cable to the skin-penetration area. These efforts resulted in suppression of systemic as well as local infection in the animal experiments.

Overview of the planned clinical study. The application for the clinical study in Japan was filed through the Ministry of Health, Welfare and Labor in June 2004. The clinical study will take place in Japan first, followed by the USA. The clinical study in Japan was planned to meet the requirement of the proposed new Good Clinical Practice (GCP) protocol that will become effective in April 2005. The sequential and parallel clinical trials in Japan and the USA will help to work out flaws in the study protocol and to establish an international network to harmonize the patient data and to optimize the regulatory process of the cardiovascular devices.

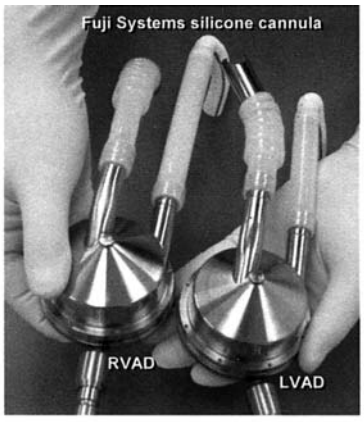
The objective of the study is thus to support the circulation of irreversible end-stage cardiac patients in whom risk of dying has increased as a result of deterioration of heart function. The study consists of the initial pilot study with a few patients to evaluate the feasibility of the study protocol and the safety of the device, followed by the pivotal study at multiple centers. The pivotal study in Japan will be conducted at four centers enrolling 20 subjects all together. The primary end-point will be to successfully bridge the end-stage cardiac patients to heart transplantation or during the 6-month support duration to demonstrate the efficacy and superiority or inferiority of the device in comparison to the existing clinical devices.

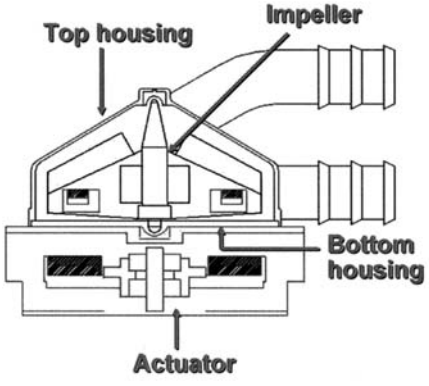
In the USA, the pilot study will enroll five subjects, followed by 100–300 subjects in the pivotal study conducted at six to ten centers. The primary end-point in the USA study is for survival of the patients until transplantation or survival for longer than 6 months aiming for bridge to transplantation as well as destination therapy.

The Miwatec/Baylor biventricular system

In phase I of the NEDO project from 1995 to 1999, the Kyocera/Baylor group worked together on a prototype pivot-bearing-supported centrifugal blood pump, the technology of which was transferred to Miwatec/Baylor in the second phase from 2000 to 2004. In the second phase, preclinical system development and validation tests were conducted. This aimed at development of a biventricular bypass system using two pivot-bearing-supported centrifugal blood pumps. The primary contractors of this project are Miwatec Co., Inc., and Softronics Co., Inc., who engineer the blood pump and actuator systems, respectively. The collaborators include Baylor College of Medicine, who validates the system both in vitro and in vivo; Hokkaido Tokai University, who engineers a transcutaneous energy transmission (TET) system; and Fuji Systems, Inc., who contributes on inflow and outflow systems.

Figure 15 shows the overall system concept of the Miwatec/Baylor biventricular MCSD.[37–45] The transcutaneously supplied electrical energy is used to actuate the implanted left and right blood pumps. The right MCSD





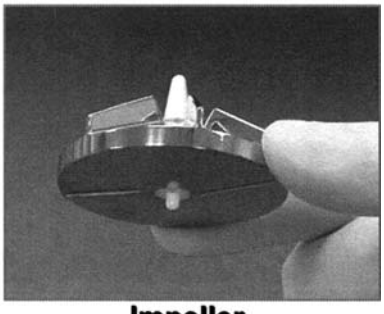


Fig. 16. Miwatec/Baylor MCSD (*top*), schematic diagram (*bottom left*), and titanium impeller (*bottom right*)

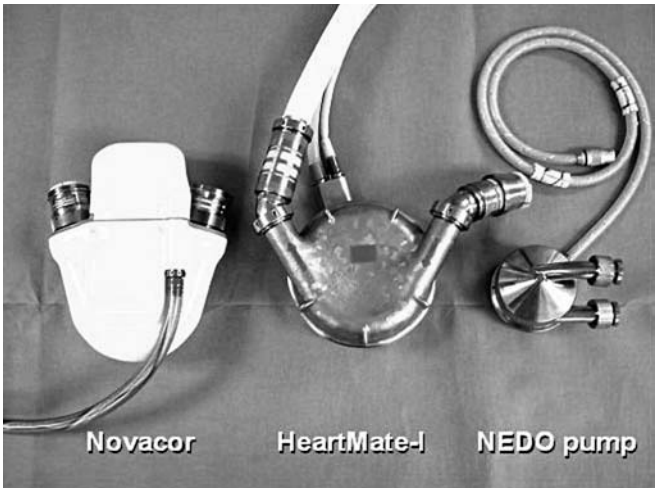


Fig. 17. Miwatec/Baylor MCSD in comparison to the Novacor and HeartMate I VE

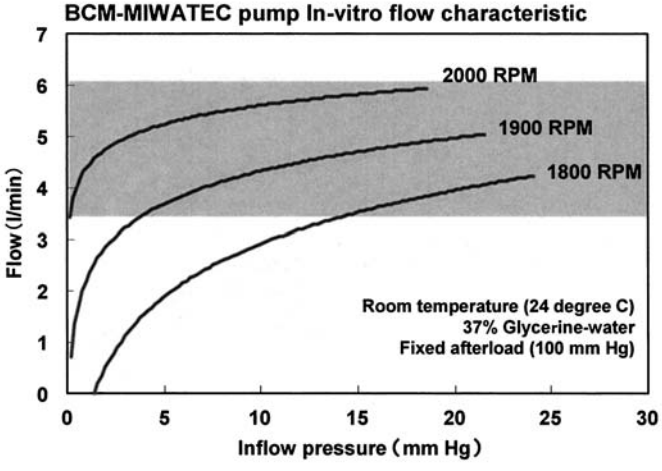


Fig. 18. In vitro flow characteristics of the Miwatec/Baylor MCSD

drains the blood from the right ventricle and returns it to the pulmonary artery, while the left MCSD drains blood from the left ventricle and returns it to the ascending aorta. Figure 16 shows the left and right MCSDs and a cross-sectional view of the pump and the titanium impeller. The impeller is supported by top and bottom pivot bearings and is rotated by a magnetic coupling force in the axial direction between the drive magnet on the motor shaft and the follower magnet on the impeller. The displacement volume is 150 cm^3 and the weight is 420 g.

In vitro system reliability study. The blood pump can deliver a maximum flow of 9 l/min at 2400 rpm, requiring approximately 6.5 W of energy. Figure 17 shows the Miwatec/Baylor pump in comparison to the Novacor and HeartMate I pumps. The in vitro hemolysis study using fresh bovine blood indicated an NIH of 0.0039 g/100 l for bottom contact mode and 0.0043 g/100 l for top contact mode. The impeller lifts off and contacts the top pivot bearing above a certain rpm; this is called top contact mode. Below a certain rpm, the impeller rotates supported by the bottom bearing,

called bottom contact mode. Figure 18 shows the pump flow as a function of the inflow pressure for different pump speeds. The pump flow increases like a pulsatile device in response to increases in inflow pressure.

The endurance test simulated the internal environment of the body by immersing the blood pump in a physiological saline bath at 37°C. A pulsatile ventricle was used to simulate the natural heart and the test pump was connected in a similar arrangement to the in vivo case. A pivot bearing accelerated durability test was also carried out. The results indicated that the expected life of the ceramic pivot bearing is approximately 10 years when used as a right MCSD and 8 years as a left MCSD. An anatomical fitting study in human cadavers has also started to improve the system design prior to clinical study.

Chronic animal study. Chronic animal studies so far have been performed in 11 half-Dexter calves with a mean duration of 59 days (22–90 days). The average left and right pump flows were 4.9 and 4.7 l/min, respectively. The average left/right pump speed was 1946/1887 rpm, requiring a power of 7.6/6.7 W. There was no thromboembolic event, but one right MCSD developed a pump thrombus caused by a kink in the outflow graft. The plasma free hemoglobin level averaged 4.7 ± 1.8 mg/dl. The antithrombogenicity of the Miwatec/Baylor pump for 3-month implantation resulted in no thrombus for either left or right pumps.

Clinical readiness study. Moving forward to clinical applications of the Miwatec/Baylor biventricular MCSD, Fig. 19 depicts three different system configurations. In Step1, defined as wearable, all the components remain extracorporeal with the inflow and outflow conduits accessing the blood from the heart and great vessels. This configuration is intended for most of the short-term support of patients, including postcardiotomy support, BTT, extracorporeal membrane oxygenator (ECMO), and percutaneous cardiopulmonary system (PCPS). In the Step 2 configuration, defined as implantable with cable, the blood pumps and actuators will be implanted inside the body with a percutaneous cable supplying the power and control signal from the external controller and power source. This configuration is

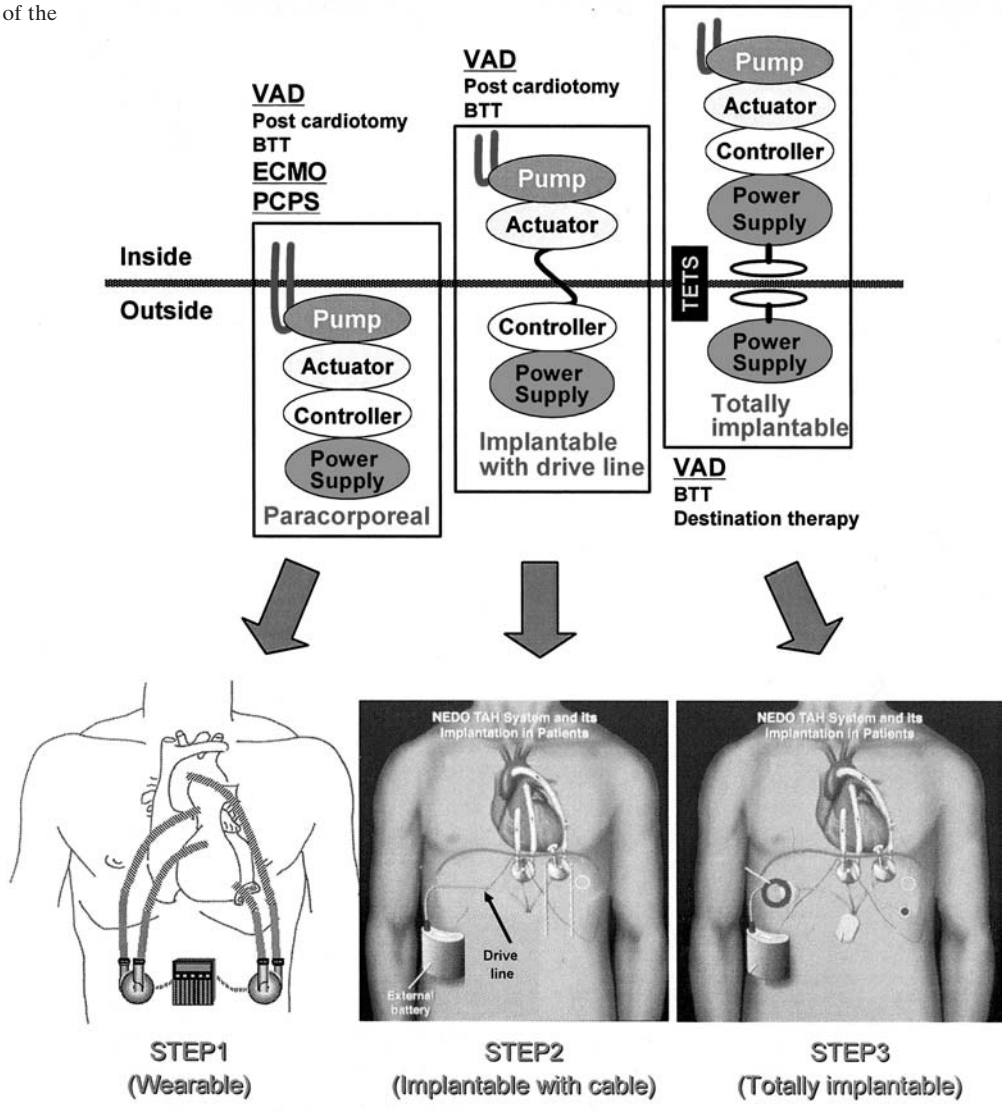


Fig. 19. Stepwise clinical approach of the Miwatec/Baylor MCSD system

intended for postcardiotomy support as well as for BTT, excluding ECMO and PCPS. In the Step 3 totally implantable system, all the components except for the power supply will be implanted inside the body and the power will be transcutaneously supplied using a TET system. The Step 3 configuration is intended for BTT, DT, or both. The blood pump configuration can be arranged in the single or the biventricular support modes. Currently, clinical teams are being formed in the USA and Europe to initiate evaluation of the system in end-stage cardiac patients.

Future directions

In dealing with future directions, several issues will be discussed, starting from device and patient selection, patient management, government regulatory processes, and industrial participation. Device development and industrial is participation a large process involving basic research, applied research, the commercialization process, and the government regulatory process. Better collaboration and systematic translation processes among laboratories, clinics, industry, and government are needed with a clear-cut objective, sufficient research and development funds, and a fair review process.

Device selection: pulsatile versus continuous flow device

The controversy continues over pulsatile versus nonpulsatile perfusion. The biventricular bypass experiment conducted during the early 1980s at the Cleveland Clinic Foundation[46–48] proved the survival of animals with a completely nonpulsatile flow. The fact that oxygen uptake in the nonpulsatile flow was identical to that of the pulsatile flow and the fact that the blood flow at the capillary level is a steady flow might suggest that a pulse may not be necessary from a peripheral perfusion point of view. Later studies[49–51] likewise demonstrated the feasibility of continuous flow for maintenance of peripheral circulation. On the other hand, the heart continuously pumps blood to the peripheral organs while supplying its own energy during the diastolic phase. The counterpulsation mode in which a higher perfusion pressure is established by a pulsatile blood pump or an IABP may help increase flow through the coronary artery for better tissue perfusion. Undar et al., from the propulsatile point of view suggested that the surplus energy contained in the pulse is key to better recovery of end-stage cardiac patients.[52–53]

The flow through the continuous flow devices, however, varies in response to changes in the ventricular pressure producing a small pulsatility. The pulsatility can be enhanced by varying the pump speed in synchrony with the heart beat and/or in combination with the effect of an IABP inserted in the aorta. We are, thus, dealing with a condition of reduced pulsatility, not a completely depulsed flow. Is reduced pulsatility acceptable from the physiological point of view to treat end-stage cardiac patients? What kind of inclusion and/or exclusion criteria are needed to select end-stage cardiac patients for treatment with the continuous flow devices?

Although we do not know the answer to these questions yet, they should be addressed by the clinical outcomes of trials using continuous flow devices. In the USA and Europe, since 2000, axial flow devices with contact bearings such as the MicroMed DeBakey VAD, the Jarvik 2000, the HeartMate II, and the maglev type Berlin Heart InCor have been used more aggressively.[54–57] Centrifugal devices such as the maglev type DuraHeart and the hydrodynamic bearing type VentraAssist and CorAide have recently moved into clinical applications in Europe and Australia.[58,59] Patients have been successfully bridged to heart transplantation, and recovery of the heart has also been reported with continuous flow devices. Isn't this evidence sufficient to accept the use of continuous flow devices in the treatment of end-stage cardiac patients?

In the future, it is recommended that a randomized trial comparing pulsatile and continuous flow devices be planned just like the REMATCH trial and other randomized trials such as CUBS and RELIANT.[60,61] Two-year survival outcome based on either pulsatile or continuous flow devices should yield an insight into the physiological consequences of nonpulsatile and continuous flow perfusion in the treatment of end-stage cardiac patients. Patient inclusion and exclusion criteria, patient management (particularly anticoagulation therapy), anti-infection regimen, and the control method of continuous flow devices in comparison to pulsatile devices could be elucidated from such a study so as to help make a decision in selecting a suitable device for patients.

Single or biventricular support, or replacement

It is said that approximately 20%–25% of heart failure patients develop biventricular failure. Biventricular bypass or replacement devices are needed to support such patients. If the recovery of the heart is possible, a biventricular bypass system is preferred to a replacement type system. Removal of the heart and implantation of a replacement device may be necessary sometimes to prevent the occurrence of thrombogenic complications inside the ventricle. The CardioWest tethered system and the tether-free totally implantable AbioCor system have demonstrated the efficacy of the replacement system in bridge to transplantation and destination therapy. In the case of a replacement device, the patient's life depends solely on the performance and reliability of the implanted device. Close to 2-year survival and improvement of patient quality of life (QOL), however, have been demonstrated by the AbioCor system in patients who had been given a prognosis of 30 days of life.[63,64] Still, thromboembolic- and infection-related complications were the main causes of death in the patients.

Again, like the Novacor and HeartMate I, the AbioCor is too large for oriental people. A smaller replacement device is needed to save patients with biventricular failure. In Japan, several TAH systems are under development including the NCVC/Aisin electrohrydraulic system under

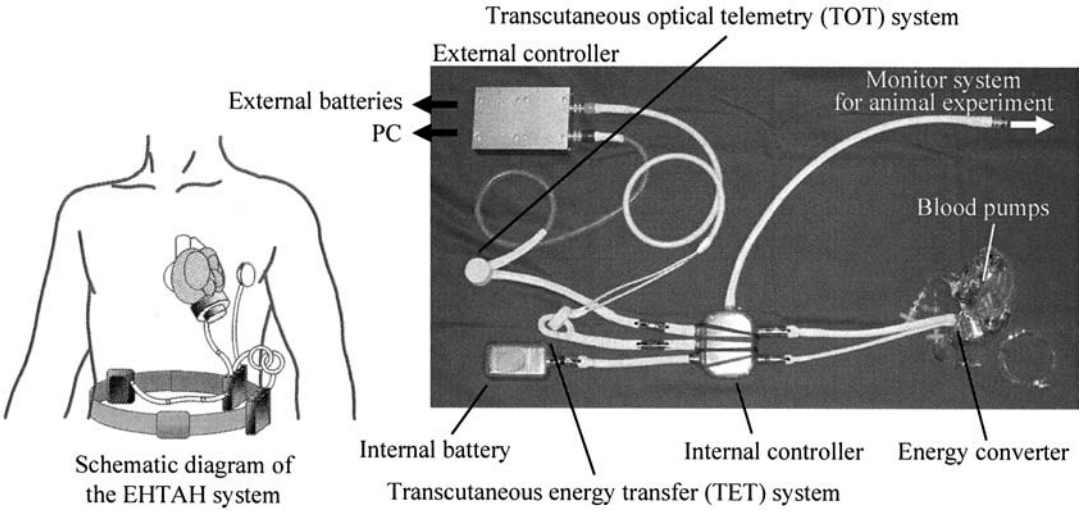


Fig. 20. NCVC electrohydraulic replacement type MCSD (total artificial heart, TAH)

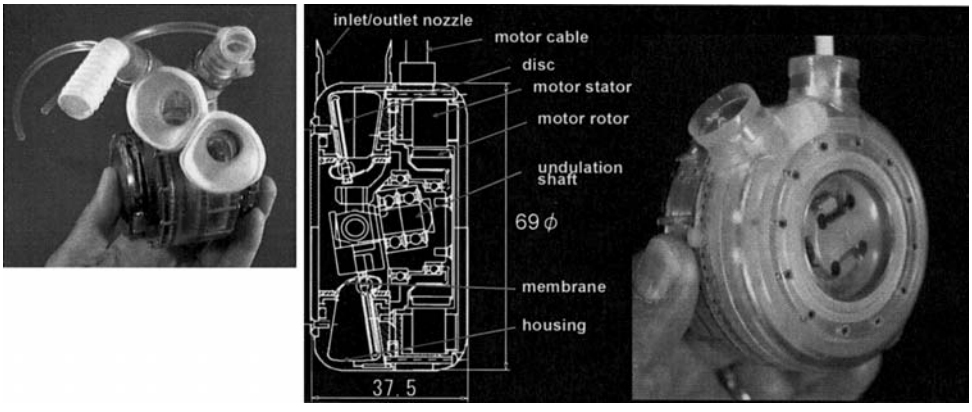


Fig. 21. Undulation type replacement MCSD (TAH, *left*) and single ventricle support device (*right*) and its mechanism developed at the University of Tokyo

Fig. 22. Electromechanical replacement type MCSD in comparison to AbioCor (*top*) and single ventricle MCSD of Tokyo Medical and Dental University in comparison to Novacor and HeartMate I VE

the NEDO project (Fig. 20); the undulating TAH of the University of Tokyo, supported by the Ministry of Health, Welfare and Labor (Fig. 21); and the electromechanical system of Tokyo Medical and Dental University (Fig. 22). Although they are still at the experimental stage, development effort must be continued to deliver an innovative system to meet future needs. Because of the severe donor heart shortage, replacement-type MCSDs can be an ideal alternative to heart transplantation, provided the technical level is improved.

The remaining 75%–80% of heart failure patients develop mainly left heart failure and a single-ventricle assist device can promote recovery as well as improve QOL. A pulsatile or continuous flow device may be chosen to treat these patients. A totally implantable, compact, durable, antithrombogenic system intended for destination therapy as well as tandem treatment in combination with drug therapy, cell and tissue transplantation, and genetic treatment is the requirement of the future. BTT can also be considered when a donor heart is available. To meet all the needs of heart failure patients, a variety of devices, including pulsatile and continuous flow devices, are needed to develop new treatment methods for heart failure and to elucidate the heart failure mechanism. From a device point of view, improvement in biocompatible and bioactive materials and improvements in durability and control of the system is the target for future innovative devices.

Bridge to transplantation, destination therapy, or bridge to recovery

As mentioned in the Introduction, the waiting time for heart transplantation exceeds 500 days in Japan because of the severe donor heart shortage. In the USA and Europe, destination therapy with MCSDs has started for those who cannot be heart transplant recipients. The US government approved the PMA and also insurance coverage for destination therapy. Because of the severe donor heart shortage situation, Japan really needs destination therapy with MCSDs. We need a more aggressive attitude in introducing and accepting new treatment options to promote QOL in end-stage cardiac patients. While the patient is supported on the device, drug therapy as well as other innovative therapies such as cell and tissue transplantation, genetic treatment, and apheresis treatment can be applied to promote the recovery of the heart as well as of other end-stage organs. The device can be removed if the heart recovers, and the patient can undergo transplantation if a donor heart becomes available; or device-dependent therapy can be continued indefinitely. For this purpose, implantable, safe, durable and reliable MCSDs, both assist and replacement types, are needed.

Device regulation and the medical industry

A new era is dawning with innovative devices appearing on the horizon. Device selection, patient selection, and postoperative patient management must be well coordinated to improve the QOL of the patients and the outcome.

The research and development of innovative devices must go on to establish smooth and better collaboration and translation among scientists, engineers, and clinicians. We need more aggressive participation of companies to promote the medical industry in Japan. The marketing of the device should be focused not only on domestic needs but also on global needs. The requirements of the whole Asia–Pacific region are going to encourage better participation and involvement of the device industry in Japan.

Finally, the government regulatory processes must be made faster for timely delivery of new technology to society. International harmonization of the regulation and patient database must be established. Personnel familiar with new technology and regulatory processes must be trained to support the growth of new technology. We all hope for the better delivery of medical care and improvement of QOL for patients.

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