Review

Beyond Implantable First Generation Cardiac Prostheses for Treatment of End-stage Cardiac Patients with Clinical Results in a Multicenter

Setsuo Takatani, DMed, PhD

After 30 years of research and development effort for both ventricular assist device (VAD) and total artificial heart (TAH) in the United States, they have been demonstrating effectiveness in the bridge to transplantation and destination therapy. Smaller size, long-term durable second generation and third generation blood pumps are now being tested in animals and moving to clinical applications. These are now combined with genetic engineering, tissue engineering and regenerative medical therapy techniques to provide newer treatment methodologies for end-stage cardiac patients. In Japan, heart transplantation was restarted in 1999, but to date only 13 transplants have been performed. Shortage in donor hearts is hindering the prevalence of heart transplantation. Over a dozen of end-stage cardiac patients are waiting for heart transplantation in hospital with a paracorporeal pneumatic VAD. Although implantable VADs have been imported from the USA, they have not acquired a wide clinical use yet because of their large size and high cost. There is a great need for development of a compact, low cost, totally implantable VAD and TAH in Japan to improve the quality of life of end-stage cardiac patients. This paper reviews the current status of the first generation pulsatile VAD and TAH as a bridge to transplantation and destination therapy around the world, followed with a review of the second and third generation blood pumps beyond the limitations of the first generation systems. Future recommendations are also discussed to improve the systems in Japan. (Ann Thorac Cardiovasc Surg 2002; 8: 253–63)

Key words: ventricular assist device (VAD), total artificial heart (TAH), bridge to transplantation, heart transplantation, destination therapy, pulsatile blood pump, non-pulsatile blood pump

Introduction

With life style changing toward a western style, occurrence of ischemic heart diseases in Japan has been increasing, resulting in more advanced heart failure cases. Also, idiopathic cardiomyopathy often leads to advanced heart failure. In order to cope with the situation, heart transplantation from brain-death subjects was legalized in 1997 and the second heart transplantation since the first transplant in 1968 was performed in 1999.[1] However, to date only 14 heart transplantations have been performed. There is a great shortage in donor hearts and also age limitation on the patient side. To find an alternative solution to heart transplantation, recently a new technique that can culture tissue and possibly a whole organ from an almighty embryonic stem cell has been receiving attention. However, it cannot meet emergency needs since it takes time to culture a tissue or organ. Artificial hearts can be available off the shelf to meet the emergency needs. Of the 14 transplanted patients in Japan since 1999, 10 were bridge to transplant from the ventricular assist devices (VAD) such as Toyobo paracorporeal pneumatic VAD, and the Novacor implantable VAD imported from the USA. Because of the bulky size and high cost involved

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with Novacor VAD (each device costs 180,000 US dollars, it has not acquired wide clinical usage in Japan. Currently over a dozen of patients are being supported with the paracorporeal pneumatic VADs and await heart transplantation while confined inside the hospital. The quality of life for these patients is questioned in comparison to freely mobile patients supported with the implantable VADs such as Novacor and Thoratec HeartMate I as demonstrated overseas. The implantable VAD patients are discharged home after recovering from the implant procedure to help improve the physical as well as emotional status and to reduce hospitalization cost. As for a bridge to transplantation or permanent circulatory support from or with a total artificial heart (TAH) in Japan, no case has been reported yet. A smaller size, low cost, implantable VAD or TAH is needed to improve the quality of life of end-stage cardiac patients for bridging to transplantation, permanent support of circulation and/or bridging to regenerative medical therapy in future. This paper reviews current status and future perspective of the implantable VAD and TAH for treatment of end-stage cardiac patients around the world.

First, Second, and Third Generation Cardiac Prostheses

Cardiac prostheses can be classified into VAD or TAH depending on its application. VAD assists the function of the failing heart without resecting the heart, while TAH anatomically and functionally replaces the failing heart. In addition, blood pumps can be grouped into either pulsatile or non-pulsatile based on its mechanism. The pulsatile devices utilize the inflow and outflow valves to pump the blood in one direction. On the other hand, the non-pulsatile devices create a unidirectional flow without using valves. The traditional and major approach in assisting or replacing the heart function was to mimic the pulsatile pumping function of the heart. These are called "first generation" devices and clinical the pumps include the Novacor and vented electric HeartMate I implantable VADs, Lion Heart totally implantable VAD, and Jarvik 7 or CardioWest pneumatic TAH and AbioCor totally implantable TAH (Fig. 1).[2-10] These devices have become commercially available after 30 years of research and development effort. In the second and third generation devices, shortcomings of the first generation devices such as size, durability, antithrombogenicity and infection resistant properties are being considered for improvement. As shown in Fig. 1, the second-generation devices are downsized centrifugal and axial flow devices with contact bearings, while the third generation devices incorporate a magnetic levitation mechanism aiming for over 10 years of durability. In this review, the status of the first generation implantable systems, including Novacor, HeartMate I VADs and CardioWest and AbioCor TAHs, applied as a bridge to transplantation and destination therapy without bridging to transplantation are thoroughly reviewed, followed by the second and third generation devices.

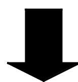
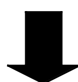
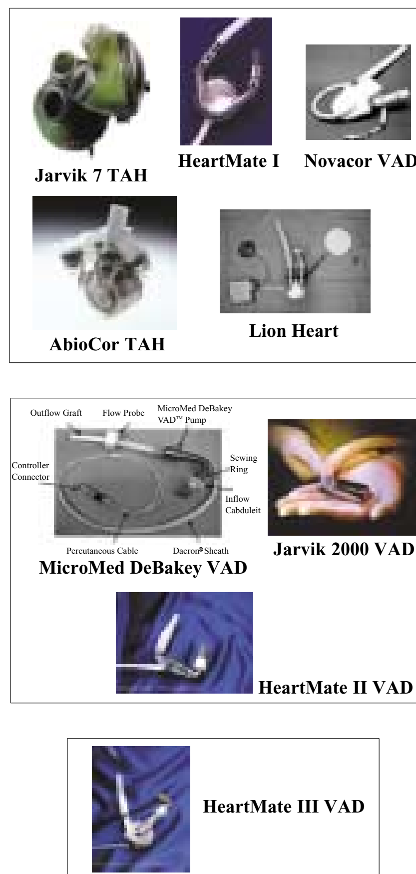

Fig. 1. First, second and third generation cardiac prostheses.

Bridge to transplantation with the implantable first generation VADs

Most frequently used first generation implantable VADs as a bridge to transplantation include Thoratec HeartMate

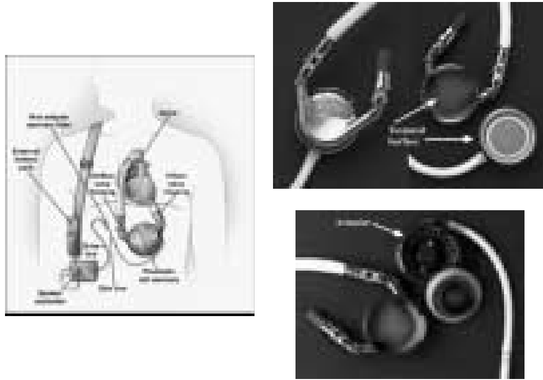

Fig. 2. Vented electric HeartMate I: anatomical configuration (left), blood pump and its blood contacting surface (right top), and actuator (right bottom).

I and World Heart Novacor VAD. Although Lion Heart is also a totally implantable first generation pulsatile VAD, it is currently used only in Europe for destination therapy in a few cases. So, it is not addressed in this review. Shown in Fig. 2 is the vented electric version of Thoratec HeartMate I. A low speed and high torque motor in combination with a face cam is used to drive the pusher-plate type blood pump having a stroke volume of 83 cc. The flexing diaphragm is made of smooth polyurethane and its surface is texturized to allow adhesion of cellular components of the blood. The pump housing is made of a titanium alloy with its blood-contacting surface textured in the same way as the diaphragm. In the inflow and outflow ports, 25 mm porcine valves are used. More than 3,000 people around the world have received the device. The longest surviving patient had the device for 1,142 days. Table 1 summarizes the multi-center evaluation of the vented electric HeartMate I VAD as a bridge to transplantation in comparison to the control group not supported with a VAD.[8] There were a total of 280 patients (232 males, 48 females) who received the VAD of which 188/280 (67%) were successfully transplanted. Post-transplant one-year survival rate was 158/188 (84%). On the other hand, among the control group who did not receive VAD, 16/48 (33%) were transplanted and post-transplant one year survival rate was 10/16 (63%). Although a small number, in 10/280 (4%) patients the device was removed due to recovery of the heart function after prolonged support. These figures indicate the apparent effect of the VAD for bridging to heart transplantation as well as for the survival rate after the transplant. The complications included bleeding 31/280 (11%), infection 113/280 (40%), neurologic dysfunction 14/280 (5%), and thromboembolism 17/280 (6%).

As for the vented Novacor VAD,[9] more than 1,100 patients around the world received the device for bridging to heart transplantation. The mean pumping duration was 254 days with 75 patients exceeding 1 year, 15 patients over 2 years and the longest duration over 4 years. It is a wearable system with the implanted blood pump connected to the external power source and controller using a percutaneous wire. The blood pump is a solenoid activated double pusher-plate system having a smooth polyurethane blood sac. In the inflow and outflow ports, 22 mm porcine valves are used. The blood pump is usually implanted in the abdominal pocket and connected between the left ventricular apex and the ascending aorta. Figure 3 shows the evolution of the Novacor system from a system having an external driving console to a totally implantable system (left), anatomical configuration (middle), and a blood pump (right). Table 2 summarizes

Table 1. Multi-center clinical evaluation of the vented electric HeartMate I as a bridge to transplantation[8]

	LVAS supported patients	Control (not supported with an LVAS)
No. patients (M, F)	280 (232, 48)	48 (40, 8)
Age (median)	11-72 (55)	21-67 (50)
Pump duration (mean)	1-691 (112) days 54/280 (19%)>180 days	
Survived	198/280 (71%)	
Transplanted	188/280 (67%)	16/48 (33%)
Post-transplanted one-year survival	158/188 (84%)	10/16 (63%)
Device removed	10/280 (4%)	
Adverse events:		
Bleeding	31 (11%)	
Neurologic dysfunction	14 (5%)	
Infection	113 (40%)	
Thromboembolism	17 (6%)	

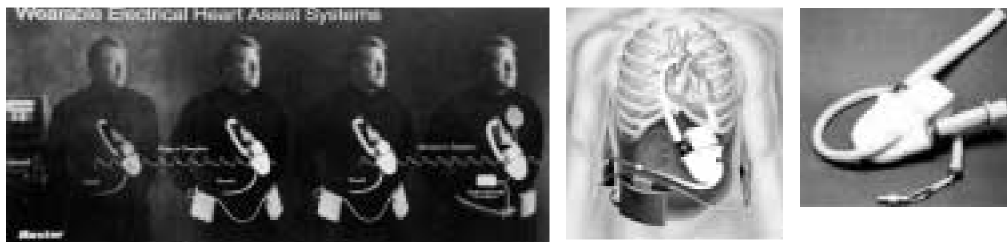

Fig. 3. The Novacor VAD: evolution of wearable Novacor system (left), anatomical configuration (middle), and the blood pump (right).

Table 2. Multi-center clinical evaluation of the Novacor VAD as a bridge to transplantation[9)]

LVAS recipients core (satisfy all entry criteria)	
No. patients	129
Mean support duration (days)	80
Transplanted	81 (77%)
Died on LVAS support	24 (23%)
Remaining on LVAS support	24
LVAS recipients, noncore	
No. patients	27
Transplanted	12 (57%)
Remaining on LVAS support	6
Controls	
No. patients	35
Transplanted	13 (37%)

Table 3. Comparison between the vented electric HeartMate I and the Novacor VAD when were applied as a bridge to transplantation[9)]

	HeartMate I	Novacor
Bridge-to-transplanted	67-72%	77%
Body surface area (m^2)	>2.0	>2.0
Patient mobility	Good	Good
Discharge home	Possible	Possible
Quality of life	Good	Good
Cost effectiveness	Good	Good
Bleeding	Lower	Higher
Thromboembolism	Lower	Higher
Device malfunction	Higher	Lower
Infection	Higher	Lower

the multi-center premarket evaluation of the Novacor VAD as a bridge to transplantation compared with the control group without VAD. A total of 129 patients received the Novacor wearable VAD, of which 81/129 (77%) were successfully transplanted, while 24/129 (19%) died on the device. Of the 35 non-VAD control group, 13/35 (37%) were successfully transplanted. Also, a small percentage of patients at around 5 to 6% recovered heart function leading to removal of the device. Like the vented electric HeartMate I, application of the Novacor is effective as a bridge to transplantation.

Table 3 compares the outcome of the vented electric HeartMate I against that of the Novacor.[9)] For a good anatomical fit of both devices, a body surface area greater than 2.0 m^2 is required, which may be too large for oriental people. The Thoratec pneumatic VAD may be applicable to smaller size patients with a body surface area of around 1.5 m^2. However, it is a paracorporeal device, limiting patient mobility and discharge-home capability. The bridge to transplant rate was approximately the same for both devices ranging from 67 to 77%. The patient mobility, quality of life and cost effectiveness were improved for both devices. The bleeding with the vented electric HeartMate I was lower than the Novacor. The thromboembolism was lower with the vented electric HeartMate I, while device malfunction and infection were lower with the Novacor. Because of the textured surface, the vented electric HeartMate I provided a better blood contacting surface, reducing thromboembolic events. However, infection rate was higher with the vented electric HeartMate I, probably due to the fact that the textured surface might have resulted in immune deficiency. This hypothesis must be tested in the future.

VAD for destination therapy: REMATCH study with HeartMate I

Although heart transplantation is an effective means in treating end-stage cardiac patients and one-year survival after transplantation is now over 80%, the major problem with heart transplantation is the requirement of donor hearts. In the USA, around 2,000 to 2,500 heart transplantations are performed annually. Because of age limitation, cost and complications such as immunosuppressive therapy, heart transplantation is limited to a small

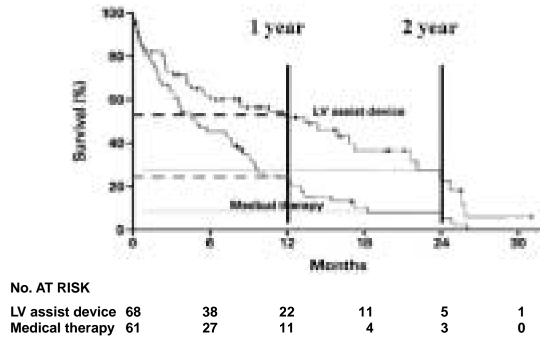

Fig. 4. Kaplan-Meier survival curve for the vented electric HeartMate patients and the control without VAD.

Liotta Heart (1969) **Akutsu Heart III (1981)**

Fig. 5. Pneumatic total artificial heart used in 1969 for the first time as a bridge to transplantation (Liotta Heart) (left) and the second bridge to transplantation application in 1981 (Akutsu Heart III) (right).

percentage of people. Forty thousand to 50,000 patients die every year with end-stage heart failure. These patients may be salvaged with the totally implantable VAD or TAH. To allow patients who are ineligible for heart transplantation to pursue surgical therapy, the destination therapy with the implantable mechanical VADs was started in 1998. The randomized evaluation of the mechanical assistance for the treatment of congestive heart failure (REMATCH) using the HeartMate I in comparison to the conventional medical therapy for the patients who are ineligible for heart transplantation was conducted from 1998 till 2001.[10,11] This study was organized under the cooperative research grant agreement among Columbia University, National Heart, Lung, Blood Institute (NIH), and Thoratec Corporation. The devices were manufactured and supplied by the Thoratec Corp. without cost to trial. The routine cost of care associated with the trial was made available by the centers for Medicare and Medicaid services and by the participating clinical centers. From 1998 till 2001, a total of 129 chronic end-stage heart failure patients who had not responded to medical treatment of the disease and who were ineligible for heart transplantation were randomly assigned to one of the two groups: 68 patients (mean age 68) to vented electric HeartMate I, and 61 patients (mean age 66) to optimal medical management.

Figure 4 summarizes the Kaplan-Meier analysis of survival of both groups. One-year survival rate with the VAD was 52%, while with the optimal medical therapy was 23%. The two-year survival rate was 25% with the device group and 8% for the medical treatment group. The quality of life as measured through emotional state, whether or not they were depressed and their mobility was much higher with the VAD group. Significant adverse events included infection, bleeding and device malfunction. The probability of infection within three months of device implantation was high at 28%. After two years, the device failed 35% of the time, with 10 patients needing a replacement. The conclusion from this study was that the use of a left ventricular assist device in patients with advanced heart failure resulted in a clinically meaningful survival benefit and an improved quality of life. A ventricular assist is an acceptable alternative therapy in selected patients who are not candidates for cardiac transplantation. One-year survival rate of 53% is lower in comparison to heart transplantation of 80%, but much better than optimal medical treatment of 25%. Through improvement in device performance, the transplant rate can be further improved. It does not require a donor heart as required for heart transplantation. Off the shelf availability of the device may meet the emergency need of 50,000 end-stage heart failure patients.

Pneumatic TAH as a bridge to transplantation

Twenty to 25% of end-stage cardiac patients exhibit biventricular failure, requiring left and right heart support. Also, left heart assist using the mechanical circulatory support device may lead to right heart failure because of increased load to the right heart. To treat end-stage biventricular failure, TAH was used for the first time in 1969 as a bridge to transplantation.[12] The Liotta Heart (Fig. 5) developed at Baylor College of Medicine, Houston, USA was used to support a 47-year old patient for three days, followed with heart transplantation. The patient expired 32 hours postoperatively. The second bridge to transplantation application of TAH took place in 1981. A 36-year

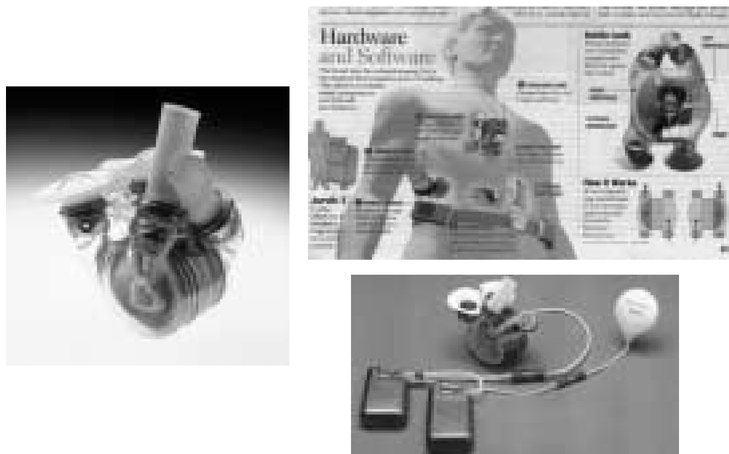

Fig. 6. Totally implantable AbioCor TAH (left), anatomical configuration (right top), and AbioCor TAH entire system (right bottom).

old patient's circulation was supported for 55 hours using the Akutsu Heart III (Fig. 5), followed with transplantation. The patient survived for eight days. These pioneering works paved the way for TAH to be used as a bridge to transplantation. The TAH intended originally for permanent replacement of the heart had found the use as a bridge to transplantation in the bi-ventricular failure patients. By late 1980's, the pneumatic TAH was used as a bridge to transplantation in more than 70 patients. From the first case of 1969 through 1991, a total of 11 different pneumatic TAH models in 221 patients at 39 centers were used as a bridge to transplantation. Of the 221 patients, 135/221 (61%) were successfully transplanted, 66/207 (32%) died while on the device, and 73/135 (54%) died following transplantation. Since 1993, the original Jarvik 7 TAH was modified as CardioWest TAH and as of September 1999, it was implanted in 114 patients worldwide, of which 24 were implanted at University of Arizona with a mean pump duration of 53 days (3-186 days) and 19/24 (79%) were transplanted and surviving. Improvement in surgical procedure, better patient management procedure helped to improve the outcome.

The destination therapy of patients with the TAH was also performed using the Jarvik 7 pneumatic TAH from 1982 to 1985 in a total of six patients.[13] The first patient, a 61 year-old dentist, survived for 112 days, followed with the longest duration of 620 days. Causes of death in this trial were thromboembolic complications and infection. Quality of life of these patients who were tethered to the external driving console and constrained in the hospital was questioned. Thereafter, the pneumatic TAH was used only as a bridge to transplantation.

AbioCor TAH clinical trials

Figure 6 shows the AbioCor TAH and its anatomical configuration in humans. The AbioCor is a one-piece device having an electrohydraulic actuator placed between the two ventricles. It is a totally contained system with the transcutaneous energy transmission system (TETs) transmitting the electrical energy inside the body to power the implanted TAH. It does not require a volume-compensating device to be implanted inside the body. A balloon implanted inside the left atrial chamber responds to the change in the left atrial pressure controlling the stroke volume of the right pump. The blood contacting surface including the pump housing, flexing diaphragm, and built-in inflow and outflow valves are made of polyurethane called Angioflex.

The Abiomed Inc. received the investigational device exemption (IDE) from the FDA in the USA, January 2001 and the first TAH implantation was performed on July 2, 2001.[14] Goals of the initial clinical trial included:

1) To determine whether the first generation of AbioCor TAH can extend life with acceptable quality for patients with less than 30 days to live and no other therapeutic alternative.

2) To learn what we need to know to deliver the next generation of AbioCor TAH, to treat a broader patient population for longer life and improving quality of life.

The patient inclusion criteria are 1) bi-ventricular failure, 2) older than 18 years old, 3) high likelihood of dying within the next 30 days, 4) unresponsive to maximum existing therapies, and 5) successful fit analysis based on AbioFit. The patient exclusion criteria include 1) heart failure with significant potential for reversibility, 2) life

Table 4. Summary of the clinical evaluation of the AbioCor totally implantable TAH for destination therapy

Patient	Sex	Age	Where	Implantation	Termination	Survival duration, causes of termination
1	M	59	Jewish hospital	07/02/2001	11/30/2001	151 days Strokes, abdominal bleeding
2	M	69	Jewish hospital	09/13/2001		391 days (10/07/2002) on-going Discharged on 03/27/2002
3	M		Texas Heart Institute	09/26/2001	02/15/2002	144 days Complications due to strokes
4	M	74	University of California	10/17/2001	12/12/2001	56 days Multi-organ failure
5	M	51	Hahnemann University	11/05/2001	08/26/2002	331 days Discharged on 01/22/2002
6	M		Texas Heart Institute	11/28/2001	11/28/2001	Death Bleeding due to coagulopathy
7			Jewish hospital	04/10/2002	04/10/2002	Death, cause not available
8-15						

expectancy over 30 days, 3) serious non-cardiac disease, 4) pregnancy, 5) psychiatric illness including drug or alcohol abuse, and 6) inadequate social support system.

To date, a total of seven implantations have been performed. Table 4 summarizes the outcome of AbioCor TAH implantation in humans. Out of seven implants, two patients have passed six-month survival and one of them is currently on-going. Although they were diagnosed to have life expectancy of less than 30 days, with AbioCor TAH their lives were extended beyond six months with a reasonable quality of life. This remarkable outcome together with VAD results reflects over 30 years of research and development efforts in the USA. Both implantable VAD and TAH can be a powerful alternative therapy to conventional medical therapy and becoming comparable to heart transplantation for the treatment of end-stage cardiac patients.

Second and Third Generation Blood Pumps

First generation pulsatile blood pumps vs. second generation blood pumps

In circumventing the shortcomings of the pulsatile devices such as size, mechanism and durability, desirable features of the nonpulsatile blood pumps are being considered for the second and third generation blood pumps. Table 5 compares the features of the pulsatile and non-pulsatile blood pumps. The non-pulsatile blood pumps can be made smaller, and its mechanism can be much simpler. They do not require heart valves as required for pulsatile devices. Thus, the non-pulsatile devices can be made at a lower cost. As for implantability of the device, the non-pulsatile devices can be easily implanted because of their smaller size. As a totally implantable system, they do not require implantation of a volume compensation device. However, non-pulsatile flow is questionable from a physiological point of view, particularly when the patient physical condition is deteriorating due to circulatory congestion. Currently, the second and third generation non-pulsatile devices are intended as a bridge to transplantation purpose. No non-pulsatile replacement device is being investigated for practical applications.

Table 5. Various features of the pulsatile and non-pulsatile blood pumps

	Pulsatile	Non-pulsatile
Blood pump		
Size	Large	Smaller
Mechanism	Complex	Simpler
Control	Complex	Simpler
Valves	Two	None
Compliance	One	None
Implantability	Complex	Simpler
Overall system	Same	Same
Cost	Higher	Lower
Physiological acceptance	OK	??

Figure 7 shows the second-generation axial flow device called Jarvik 2000 blood pump in comparison to the first generation HeartMate I VAD.[15] Also shown in the figure is the anatomical configuration of the device as a totally implantable system. It is an axial flow pump that can be inserted in the left ventricular apex to assist the failing left ventricle. This device has been implanted in a patient for a two-year duration with the power being supplied using a percutaneous line through a skull. A stable,

Fig. 7. Jarvik 2000 second generation VAD in comparison to the vented electric HeartMate I (left), anatomical configuration for the implantable system with a percutaneous lead (middle top), implantable system with a TET system (middle bottom), and implantable system with a percutaneous line penetrating through the skull (right).

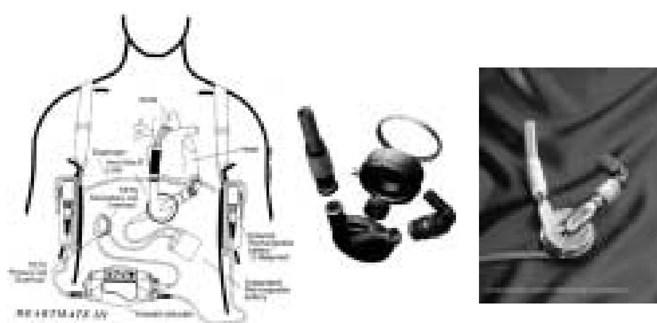

Fig. 8. HeartMate III third generation blood pump: anatomical configuration (left), pump system assembly (middle), and HeartMate III (right).

noninfectious performance can be obtained for a prolonged duration (Fig. 7). Besides the Jarvik 2000 blood pump, there are also second-generation devices called MicroMed DeBakey VAD[16,17] and the Thoratec HeartMate II[18] (Fig. 1). Common feature in these blood pumps is the contact bearing that supports the rotating impeller. However, wear of the bearing mechanism limits the operational life of the device. The nominal life of these second-generation blood pumps is estimated to be around five years. All these devices are now being used as a bridge to transplant applications in the end-stage cardiac patients, demonstrating a promising result.

Second generation vs. third generation system

Beyond the first and second-generation blood pumps, the third generation blood pumps are now being investigated. The main feature of the third generation blood pump is the magnetic levitation to eliminate contact bearing that supports the impeller in the second-generation blood pumps. Since there will be no wear due to friction effect at the contact bearings, life expectancy of the third generation blood pumps is expected to be beyond 10 to 15 years. Figure 8 shows the Thoratec HeartMate III magnetically levitated third generation centrifugal blood pump.[19] The impeller is completely suspended in the magnetic field without any contact bearings. Magnetically levitated axial and centrifugal blood pumps based on other concept are also under development in the USA and Europe.[20,21]

Artificial Heart Development in Japan

Although artificial heart research goes back to early 1960's in Japan, nationally supported projects did not start until late 1990's. In 1995, the Ministry of Health, Welfare and Labor, Ministry of Economics and Industry (MEI) and Ministry of Technology and Science (MTS) all independently launched the national artificial heart projects. Under MEI, the New Energy and Industrial Technology Development Organization (NEDO) supports the Aishin/National Cardiovascular Center (Aishin/NCVC) TAH project and Miwatek/Baylor College of Medicine bi-ventricular bypass system project. This project is now in the phase II stage to evaluate the long-term durability prior to chronic animal evaluation. Figure 9 shows the Aishin/NCVC TAH system and its anatomical configuration.[22] It is a low-pressure electrohydraulic system with the en-

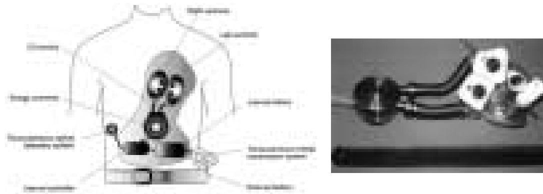

Fig. 9. National Cardiovascular Center TAH anatomical configuration (left), and TAH system (right).

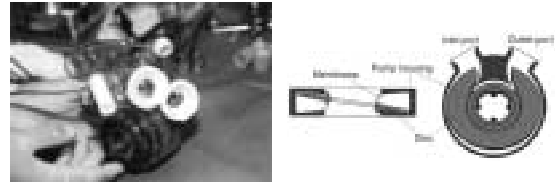

Fig. 10. University of Tokyo TAH system (left) and its assembly diagram (right).

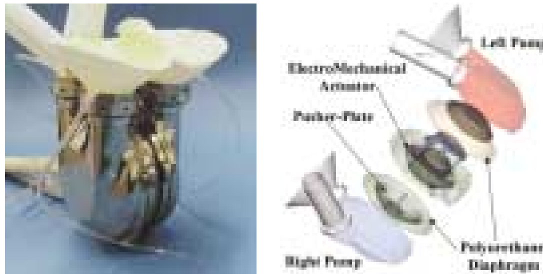

Fig. 11. Tokyo Medical and Dental University TAH (left) and its assembly diagram (right).

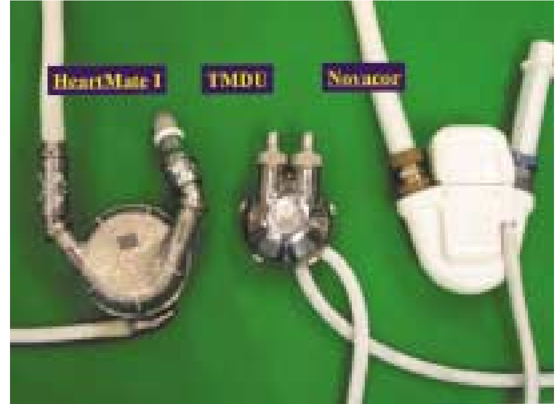

Fig. 12. Tokyo Medical and Dental University VAD (middle) in comparison to the vented electric HeartMate I (left) and the Novacor VAD (right).

ergy converter implanted in the abdominal area. The left and right heart output is balanced by inserting a shunt between the two atrial chambers. The entire system is intended for implantation in 50-60 kg adults. Another system under evaluation in animals is the undulation type TAH developed at University of Tokyo[23] (Fig. 10). Figure 11 shows the one-piece left-right alternately ejecting, electromechanical TAH under development at Tokyo Medical and Dental University (TMDU).[24,25] The pumping unit was designed to fit in 50-60 kg adults based on the anatomical data obtained from 26 heart transplant recipients in the United States. Although it was miniaturized to yield a volume of 400 cc, it provided the maximum flow of 8 L/min against the left afterload of 100 mmHg. The blood contacting surface was coated with an antithrombogenic MPC polymer that mimics the lipid layer of the biological membrane.[26] This system is now under evaluation in a chronic animal study. Shown in Fig. 12 is the electromechanical VAD (middle) also under development at TMDU utilizing the same components as those of the TAH.[27] The diameter and thickness of the pump are 90 mm and 56 mm, respectively, yielding an overall volume of 275 cc and weight of 450 g. Although it was considerably downsized in comparison to the Novacor and HeartMate I, it provided a maximum flow of 8 L/min against an afterload of 100 mmHg. This device should be ready for clinical use in two to three years after evaluation in animals for its antithrombogenicity, durability and controllability. As for continuous flow devices in Japan, Terumo Co. magnetically suspended centrifugal blood pump[28] and Sun Medical Inc. purge system centrifugal blood pump[29] developed under the NEDO and Agency of Technology and Science, respectively, are both under premarket evaluation abroad and they will be ready for clinical use within a year or so.

Future Recommendation

Currently, we have two paracorporeal, pneumatic VAD systems approved for clinical use by the Ministry of Health, Welfare and Labor. However, these technologies are approximately 10 years old. We should replace these technologies with the new ones to improve the quality of life of patients. It is a great disappointment to see the patients supported with paracorporeal devices, confined

inside the hospital while waiting for donor hearts. From the point of improving the patients physical as well as psychological status, and to reduce hospitalization cost, development of a smaller size, low cost, implantable device is of an emergent need. Particularly, shortage in donor hearts strongly suggests permanent use of VAD. Long-term durable, antithrombogenic, infection resistant VAD is needed to bridge the patients to heart transplantation, bridge to recovery or bridge to regenerative therapy in future. Successful application of the VAD will establish a reliable base for future clinical application of the permanent TAH in Japan.

Why is it so difficult for the implantable artificial heart systems to be successfully commercialized in Japan, although we have enough technological background? In answering this question, first of all, we must have a unified strong policy to organize various government agencies from research, development, pre-clinical testing, premarket evaluation, to the manufacturing process. A well-defined target must be formulated for the next five to 10 year period. Second, sufficient funding must be provided to selected groups through a screening process, not dividing among many groups. Third, industrial involvement is a priori requirement for successful commercialization and encouragement of a venture business. In addition to government policy, funding and industrial participation, we need also a thorough review process. An adhoc peer review committee must be organized by gathering experts in each field to periodically check the project for proper execution of the research plan and grant. Finally, the regulatory process for premarket process must be re-evaluated to meet international standards. The estimated number of patients who might need some kind of circulatory support in the 21st century are increasing year by year. According to the survey by the Institute of Medicine report in 1991,[30] in 2020 the number of congested heart failure patients under 80 years old who may need artificial heart systems is estimated to be around 100,000 per year. Artificial hearts can meet the needs of these patients by offering a wide scope of therapies such as 1) bridge to heart transplantation, 2) bridge to recovery, 3) bridge to regenerative medical therapy, or 4) as a destination therapy.

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