Ventricular assist device applications

Ventrikül destek cihazi uygulamaları

Kerem M. Vural

Department of Cardiovascular Surgery, Türkiye Yüksek Ihtisas Hospital, Ankara, Turkey

Abstract

Since the commencement of the artificial-heart program at the National Institutes of Health in 1964, many circulatory-support devices have been developed for short-term use in patients with end-stage heart failure. In the last decade, the interest on mechanical devices for ventricular assistance increased rapidly. As a result, significant advances in both the technology and clinical experience in the field of mechanical cardiac assist occurred over the last decade. In the current era, there is a wide variety of devices both available and in development. This article briefly reviews the evolving concepts and current systems on ventricular assist devices, as well as their role in today's clinical practice.
(Anadolu Kardiyol Derg 2008; 8: Suppl 2; 117-30)
Key words: Heart-assist devices, ventricle-assist device, heart, artificial, artificial organs, cardiac failure, cardiomyopathy

Özet

Yapay kalp programının 1964 yılında National Institutes of Health tarafından başlatılmasından sonra son dönem kalp yetmezliğindeki hastalarda erken dönemde kullanım için birçok dolaşım destek cihazları geliştirilmiştir. Son 10 yılda, mekanik ventrikül destek cihazlarına ilgi hızla artmıştır. Sonuç olarak son 10 yıl içerisinde, mekanik kalp desteği alanında hem teknoloji, hem de klinik deneyim açısından önemli gelişmeler ortaya çıkmıştır. Çağımızda, gerek mevcut, gerekse gelişme aşamasında çok çeşitli cihazlar bulunmaktadır. Bu makale kısaca, ventrikül destek cihazları üzerine gelişmekte olan konseptleri ve halihazırdaki sistemleri, ve bunların günümüz klinik uygulamadaki rollerini gözden geçirmektedir.
(Anadolu Kardiyol Derg 2008; 8: Özel Sayı 2; 117-30)
Anahtar kelimeler: Kalp-destek cihazları, ventrikül-destek cihazı, kalp, yapay, yapay organlar, kalp yetersizliği, kardiyomiyopati

Introduction

According to the Registry of the International Society for Heart and Lung Transplantation: Twenty-fifth Official Adult Heart Transplant Report-2008, at the time of transplant, almost 29% of patients were on some type of mechanical circulatory support modality (22% on left ventricular assist device-LVAD) (1). This is a significant increase compared to the previous reports. Heart disease continues to be the leading cause of deaths worldwide (1). Congestive heart failure affects more than two million patients and causes approximately 400.000 deaths annually in the United States. Status-1 patients have an annual mortality over 65%. The overall mortality for patients on the transplantation waiting list is about 30% per year. Apart from this group suffering deeply from donor shortage, there is also another group consisting of those who cannot be weaned off cardiopulmonary bypass at the end of an open-heart procedure (postcardiotomy failure).

In the last decade, the interest on mechanical devices for ventricular assistance increased rapidly (2). This is partly because of the growing need for a means to bridge the patients with end stage heart failure to transplantation, where donor availability is long overwhelmed by the increase in patient number on the transplant waiting list. In addition, the reported long-term success with device support, pointed out to the possibility of permanent cardiac assist. As a result, significant advances in both the technology and clinical experience in the field of mechanical cardiac assist occurred over the last decade.

Address for Correspondence/Yazışma Adresi: Kerem M. Vural, MD, FETCS, N. Tandoğan Cad. 5/6 06540 Kavaklıdere, Ankara, Turkey
Phone: +90 312 306 17 10 Fax: +90 312 426 61 81 E-mail: kvural@tr.net

In the current era, there is a wide variety of devices both available and in development, ranging from simple, percutaneous, left-sided support systems to totally implantable artificial hearts. New support systems have been developed and are being tested for both bridging and supporting purposes. This article briefly reviews the evolving concepts and current systems on ventricular assist devices, as well as their role in today's clinical practice.

Historical notes

The first clinical successful device implantation took place in 1963 by Hall and colleagues (3). This was an intracorporeal device supporting the left-sided circulation and employed two cage-ball mechanical valves to ensure one-direction blood flow. A paracorporeal device was developed shortly after, and successful clinical results with explantation and discharge were reported (4). These devices were developed for short-term support for postcardiotomy failure patients, a group of potential ventricular assist device (VAD) candidates that appeared with the introduction of open heart surgery into clinical practice. In 1964, the National Heart Lung and Blood Institute started an "artificial heart program". With the extension of this program into 1970s, the "Medical Devices Applications Branch of the National Heart and Lung Institute", aimed to develop mechanical devices for both short-and long- term purposes, as well as total artificial hearts (5, 6). The contractors, including Abiomed, Baxter, Thermo Cardiosystems and Thoratec Labs., subsequently entered into the development process. Successful bridging of patients to transplantation were reported first using a total artificial heart in 1969 (7), then with a left ventricular assist device in 1978 (8). With the reintroduction of heart transplantation owing to new immunosuppressant regimens, candidates on the waiting lists demanded development of better devices for mechanical heart assist for increasingly longer periods of support. Consequently, investigational use of two devices intended for long-term support to bridge transplantation according to NHLBI program was approved by the United States Food and Drug Administration (FDA). These were the Novacor (then Baxter Healthcare Corp, Berkeley, CA) and HeartMate (then Thermo Cardiosystems, Woburn, MA) implantable systems. The pneumatic version of the HeartMate (IP model) was the first device approved for general clinical use in 1994. The survival and quality-of-life benefits of these devices along with the ability to discharge LVAD patients home and resume work while awaiting heart transplant were soon appreciated (9). In 1994, National Institutes for Health issued another request for proposal, this time for "Innovative Ventricular Assist Systems." Accordingly, newer generation devices including axial flow pumps and centrifugal pumps were developed. The main advantages of these devices included easy application, total implantability, small sizes, quiet operation and better reliability. Meanwhile, with prolonged unloading of the failing ventricle by the newly developed longer-term assist devices, some reverse remodeling of the diseased myocardium was observed. This pointed out to other potential uses of assist devices, such as long-term unloading and then explantation without transplant (11), or permanent implantation as a destination therapy for end-stage patients who are not transplant candidates (12).

As a pioneering cardiac surgery center in Turkey, our institution felt a need for a short-term assist device for postcardiotomy failure patients during 1960s and 1970s, and roller pumps or short-term centrifugal pumps were then used to support circulation in these patients. In 1989, the first Jarvik-7 device insertion in Turkey took place in Ankara University, and the patient was supported for a period of 31 days until his death due to multiple organ failure (13). In 1990, a new biventricular assist device, Abiomed BVS 5000, entered service in our institution, Yüksek İhtisas Hospital of Turkey, and was used in postcardiotomy failure patients with limited success. As a consequence of evolving cardiac bio-assist concept during 1990s, our clinic started a skeletal muscle dynamic cardiomyoplasty program in 1993 and some patients were subsequently bridged to transplantation (14). In 2001, the first successful clinical long-term assist device application in Turkey was performed in Yüksek İhtisas Hospital of Turkey. Three patients were inserted with DeBakey axial flow pumps, two of them were successfully bridged to transplantation, one of them still alive.

Patient selection

Indications for assist device implantation

The first clinical applications of ventricular assist devices merely aimed to support a ventricle failing after an open-heart procedure (postcardiotomy failure). The goal was to support circulation for a few days or weeks, in an expectation of some recovery in myocardial contractility. The physiological repair of reversibly damaged contractile elements (e.g. recovery of the normal response to calcium ions) and restoration of the consumed ATP reserves by de novo synthesis (since faster salvage pathways cannot be used in the local absence of precursor nucleotides) usually require days. The recovery of other systems (such as kidneys) that may be damaged during the low output state also necessitates a sustained, adequate circulation supplying nutritients, oxygen and precursors for repair. Although rare in today's clinical practice, there are still patients who can not be weaned off from cardiopulmonary bypass at the end of an open-heart procedure. The Norman criteria established in the early era of ventricular assist still apply in decision making for "when to support?" Despite maximum inotropic support and intra-aortic balloon counter pulsation, if the patient's cardiac index is below 2 lt/min/m^2 BSA, pulmonary capillary wedge pressure is over 20 mmHg, and the systolic blood pressure is below 80 mmHg, then a ventricular assist device should be used (15).

In addition to these patients requiring short-term support, there are others who may benefit from long-term circulatory assist. The assist device implantation indications may vary in this less homogenous group, which includes the patients with reversible heart diseases such as myocarditis (bridging to

recovery), those waiting for a suitable donor organ (bridging to transplantation) and still others suffering from irreversible, end-stage heart failure who are not transplant candidates for some reason, therefore in need of permanent mechanical support (destination therapy). As pointed out in an article by Di Giorgi et al, different indication groups may benefit from different devices (16). In conclusion, the major indication groups for VADs are: 1- Short-term transient support of the circulation, as in the cases of postcardiotomy failure (17), acute respiratory distress syndrome, acute (especially anterior wall) myocardial infarction (18), high-risk percutaneous coronary intervention (PCI), post-transplantation reperfusion injury etc. 2- Bridging: a) Bridge to transplantation (BTT) (19); b) Bridge to recovery (BTR), prolonged but transient circulatory support, for example until recovering from a myocarditis etc. c) Bridge to bridging (BTB, i.e. for short-term support until a more sophisticated long-term device can be inserted) 3- Permanent implantation (Destination therapy or alternative-to-transplant ATT) (20-23).

Indications for total artificial heart insertion

The indications of total artificial hearts somewhat differ from those of assist devices (23-26). The implantation of a total artificial heart necessitates total or near-total cardiectomy, rendering any future explantation impossible. Therefore, the initial enthusiasm about these devices faded quickly. The a ctual use of total artificial hearts are usually limited to the patients that are not considered as a good candidate for LVAD implantation due to anatomical/physiological impediments such as: 1- Endocarditis-with cardiectomy, a constant source for blood borne infection is eliminated. 2- Malignant cardiac tumors - allows for resection of the malignancy. 3- Graft vasculopathy following cardiac transplantation - in which a LVAD implantation is not feasible due to both immunosuppression and extensive nature of the disease (right ventricle involvement). 4- Severe biventricular failure necessitating long-term support. 5- Severe pulmonary hypertension, which both exacerbates with the implantation and impedes the LVAD function. 6- Large congenital intracardiac shunts. 7- Prosthetic aortic valves, which constitute a nidus for thrombi in the presence of an LVAD. 8- Large left ventricular thrombus or aneurysm and apical fresh infarct, due to potential problems with apical insertion of LVAD inflow cannula and also for being a thromboembolic source. 9- Untreatable or unresectable source of sustained ventricular arrhythmia disturbing right ventricular function, which is essential for LVAD filling in the early postoperative period.

Contraindications of ventricular assist device insertion

It is difficult to draw absolute contraindications for a life-supporting device, where not using it may result in the patient's demise. Therefore, the contraindications are often considered as relative rather than absolute. Perhaps the term "risk factors" is more appropriate. Furthermore, these issues are still controversial and subject to constant evolution. In general, the patients with severe pulmonary disease (27, 28), blood dyscrasias (28), psychiatric disorders (in which suicidal attempts can be successful by simply unplugging the device or incompliant behavior may interfere with device function) and irreversible organ dysfunctions are not good candidates for mechanical assist devices. A small body surface area precludes the implantation of bulky devices such as HeartMate VE, and also creates a tendency to thrombosis due to low preset flow rates, especially when the body surface area is less than 1.5 m² (29). Severe aortic valve insufficiency produces a "vicious-circle circulation" and device output returns again and again to the left ventricle via the incompetent aortic valve. Any right ventricle dysfunction, caused by irreversible ischemia, myocarditis, cardiomyopathy, damage to essential coronary grafts, or any situation impairing left ventricular filling such as severe pulmonary hypertension will eventually lead to the failure of a left-sided device due to filling compromise. Therefore, in such circumstances, any left ventricular assist device should be avoided. Most LVAD inflows are apically inserted, and the presence of a fresh apical infarct may preclude device insertion. Large left ventricular aneurysms can be sucked into the inflow cannula with devastating consequences (30). Active gastric/intestinal ulcer disease or infection is also among the contraindications for device insertion.

Risk factors

The patients in relatively greater risk rendering them less-than-ideal candidates for assist device insertion are those with: 1- an urine output less than 30 mL/hour; 2- a serum creatinine level exceeding 5 mg/dL; 3- a high initial central venous pressure in the presence of a relatively low pulmonary artery pressure; 4- mechanical ventilator dependence (interfering with left ventricular filling); 4- a refractory coagulation disorder with a prothrombin time exceeding 16 seconds (which may expected to worsen after implantation and pointing out a right ventricular dysfunction and subsequent hepatic insufficiency, both indicating poor prognosis; 5- reoperation, especially if damage to right ventricle or right ventricle-supplying coronary grafts is possible; 6- an infection of undetermined/unknown origin; 6- serum bilirubin increase; 7- preimplantation extracorporeal membrane oxygenation (ECMO)-dependence.

Some issues to address for subsequent device placement

Cardiac issues: Right ventricular failure is the cause of mortality in about 20% of LVAD recipients. To predict possible postimplant right ventricular failure, preoperative right ventricular stroke work may be used as a parameter (31). Severe aortic regurgitation should be addressed during LVAD implantation (see above) (32). At times, oversewing the valve may be necessary. A severe aortic stenosis should always be corrected before permanent cardiac replacement because these patients often have adequate myocardial reserve, even

with very low preoperative ejection fractions and severe congestive heart failure (28). If a prosthetic valve replacement is necessary, mechanical prostheses should be avoided because of the increased rate of thromboembolic complications. Mitral insufficiency is not an important issue since after LVAD insertion the left ventricle is completely unloaded and the end-diastolic pressure approaches to zero. On the other hand, mitral stenosis should be corrected since it may interfere with LVAD filling (28). Tricuspid insufficiency should be treated because LVAD filling and success depend on right ventricular forward flow. The LVAD recipients with coronary artery disease can still have angina or ischemic myocardial injury if this is not surgically addressed or if the atherosclerotic disease is inoperable. Sometimes antianginal medication becomes necessary. Any previously constructed coronary grafts, especially if they are supplying right ventricular territory, should be protected. Atrial or ventricular septal defects should be repaired at the time of device placement in order to avoid desaturation due to increasing right-to left shunting after LVAD insertion (33).

Extracardiac Issues: Preoperative normalization of coagulation parameters, with a prothrombin time less than 15 seconds, and restoration of normal transaminases and bilirubin are of pivotal importance in potential LVAD recipients who may have hepatic congestion and dysfunction preoperatively (28). All patients should have a detailed neurological and psychiatric assessment to ascertain whether the patient will overcome the physical and mental problems associated with device support (27). Potential LVAD recipients should be checked for their nutritional status and may need days or weeks of intensive nutritional supplementation. Physical therapy and rehabilitation may also become ne cessary in end-stage heart disease to re-establish muscle mass and strength. Severe peripheral vascular disease, especially severe iliac artery disease complicates LVAD placement (by interfering with femoral cannulation), maintenance (by interfering with continuous arteriovenous hemofiltration to manage patients with renal insufficiency) and removal (by interfering with intraaortic balloon insertion). Severely diabetic patients are at high risk of infection and often not considered as future transplantation candidates. The possible LVAD recipients should be screened carefully for pre-existing evidence of infection. A confirmation for the absence of positive blood cultures, especially for fungi, a week before device insertion is essential. All actual sources of infection must be completely treated. Prophylactic antibiotic use is mandatory (see later in the text).

Device selection

Currently, there is a wide spectrum of available or developing devices, ranging from percutaneously inserted, simple left-sided systems to fully implantable total artificial hearts. The device selection is of pivotal importance for success and should be done carefully on an individual basis.

I- Ventricular assist devices

a) Paracorporeal devices

This group consisted of uni-biventricular paracorporeal/extracorporeal assist devices and total artificial hearts controlled by an extracorporeal console. The latter will be discussed elsewhere.

1) Short-term support devices
Apart from the centrifugal pumps such as BioMedicus (Medtronic, Inc., Minneapolis, MN) and the Sarns/3M Centrifugal System (Sarns/3M, Ann Arbor, MI) which can be used for short-term transient use for postcardiotomy failure, ECMO or bridge to bridging (BTB, i.e. for short term support until a more sophisticated long-term device can be inserted) purposes, a good representative of this group is the Abiomed BVS 5000 (Abiomed Cardiovascular, Inc, Danvers, MA) device. The first human application was in 1987 and followed by more than 3000 implantations. This device is both FDA- and CE-approved for postcardiotomy failure or bridging. It is often used for transient short-term right ventricular support during left ventricular assist with another device such as HeartMate (Thoratec Laboratories Corp,

Pleasanton, CA) or for bridge to bridging, in today's clinical practice. The BVS 5000 system is actually a biventricular support device, with both the pump chambers and control console are paracorporeal (i.e. externally situated at the side of the patient). It is relatively cheap and simple to insert but generally considered for short-term-use. The drive system is an electro-pneumatic device using synthetic valves to ensure one-way blood flow.

2) Long-term support devices
Thoratec (Thoratec Laboratories Corp, Pleasanton, CA) PVAD system (first human application in 1982) is another pneumatically driven, paracorporeal uni/biventricular assist device for possibly longer periods of support (weeks, months), allowing for better patient mobility. It is a more sophisticated device generally considered for long-term uni/bi ventricular support, which is essential for bridging to transplantation. However, it is more expensive and both implantation and maintenance are not as simple as BVS 5000. It consists of an externalized pneumatic pusher-plate pump positioned subcostally and connected to a drive console. The HeartMate IP (Thoratec Laboratories Corp, Pleasanton, CA) device is another pneumatically-driven, univentricular and implantable device. Based on work started in the mid-1960s, the first clinical implantation of the HeartMate took place in 1986. The HeartMate was the first mechanical circulatory support device to be approved by the FDA as a bridge-to-transplant. The IP model is the pneumatically driven implantable version but there is also an electrically powered (vented electric -VE) version. The bulky pump chamber is implanted intracorporeally and connected to an extracorporeal control console (IP) or a wearable battery and control unit (VE/XVE). Berlin Heart (Berlin Heart GmbH, Germany) Excor (first human application in 1990)

and Abiomed AB 5000 (first human application in 2003) systems are newer examples of paracorporeal, pneumatically driven uni/bi ventricular assist devices for bridging-to-transplantation purposes. All these devices are driven and controlled by a paracorporeal pneumatic consol of varying transportability. The newly developed more versatile Thoratec IVAD is designed to be an implantable and home-dischargeable biventricular assist device indicated for postcardiotomy failure recovery and bridge-to-transplantation.

b) Implantable (intracorporeal) systems

This includes implantable left ventricular assist devices (LVADs) and implantable total artificial hearts (TAHs). There is some controversy in the use of term "implantable" here, since some of the systems presented below are only partially implantable (i.e. the main pump chamber is intracorporeal and connected to a wearable/portable external battery and control unit by a driveline or cable piercing the skin) while some others are totally implantable.

1) Left ventricular assist devices
This is a heterogeneous group consisting of devices developed in different periods, employing different drive mechanisms, inspired by different principles. It is best to review them under three generation groups:

1-First generation: These are implanted, pulsatile, electric-driven, bulky, pusher-plate displacement pumps connected to a wearable, control and battery unit by a driveline piercing the skin, allowing discharge to home on support. The first FDA approved devices for permanent use (destination therapy) are from this group. These two well- known devices are the Novacor N1000PC (World Heart, Inc., Oakland, CA) and HeartMate VE (Thoratec Laboratories Corp, Pleasanton, CA) (electrically-driven version of HeartMate) systems. They were used extensively for both bridging and permanent purposes on an outpatient basis. The main drawbacks of the Novacor system was anticoagulation necessity and a relatively high incidence of thromboembolic events (29) while infection and technical problems were more commonly observed problems with the HeartMate system. The blood-device interface of the HeartMate pump incorporates titanium microspheres and the flexible diaphragm is covered with textured polyurethane. This unique structure promotes the formation of a pseudo-intimal layer densely attached to the interior surface of the device, and may be responsible for the low thromboembolic risk (less than 5%) associated with the HeartMate despite the lack of anticoagulation (35). The Novacor device, on the other hand has an excellent mechanical reliability (36), however mandates strict anticoagulation with coumadin (INR 2 to 3) and aspirin (29). With growing experience, it is realized that the LVAD driveline piercing the skin to connect the implanted pump to an extracorporeal control and battery unit is problematic in many ways, including infectious complications and technical problems (37). To overcome such problems associated with

this driveline, a wireless transcutaneous energy transfer system (TETS) has been developed. Many newly developing fully implantable devices of different genres are expected to use this new technology. The newest member of this family, the Novacor II (World Heart, Inc., Oakland, CA) device is an improved version of Novacor and is still in its preclinical development stage.

2-Second generation: These are mainly named as "axial flow pumps". Employing the "Archimedes' screw" principle, these pumps use electrical energy to rotate an axle on which a turbine or propeller system is mounted to propulse liquids forwardly. A very high rotation rate makes it possible to pump large amount of blood in accordance with the body needs. These systems consist of a much smaller pump with fewer moving parts and less blood-contacting surface than pusher-plate devices. However, the system works on high rotational speeds (38), heat is generated, hemolysis with damage to the blood cells and thrombi may occur (39). Anemia and platelet damage along with the activation of contact coagulation system may ensue. All these can interfere with device function, and cause thromboembolic complications (40). In addition, the flow they provide is non-pulsatile (or with the contribution from the patient's own heart "less pulsatile"), and this non-physiological condition, although well tolerated by mammalian organisms after a period of adaptation (41), may cause compromises and distorting effects in baroreceptor activity, catecholamine release, lymphatic pump, renal cortical blood flow, fluid shift and vascular wall structure integrity in the early period of implantation. With the use of these devices, myocardial oxygen consumption is reported to decrease by 20% and coronary perfusion pressure is expected to increase. Since there is no one-way valve mechanism employed on these devices, any device malfunction leads to develop the equivalent of wide-open aortic insufficiency. Among these devices are the HeartMate II (formerly Nimbus) (Thoratec Laboratories Corp, Pleasanton, CA), Micromed DeBakey VAD (MicroMed Cardiovascular, Inc Houston, Texas), Berlin Heart INCOR (Berlin Heart GmbH, Germany) and Jarvik 2000 FlowMaker (Jarvik Heart, Inc., New York, NY) systems, weighing between 53 and 176 g rams.

DeBakey VAD: This axial flow pump was developed by Drs. Michael E. DeBakey and George P. Noon with the collaboration of NASA engineers in 1988 (conceptual work) and licensed in 1996 with the first clinical application in 1998. Since then it is used extensively mainly in Europe, with a longest assist period over 500 days. It is also the first successful long-term left ventricular assist device implanted in Turkey in 2001 at Yüksek İhtisas Hospital of Turkey. Initially three devices were implanted in this clinic and two were successfully bridged to transplantation; one is still alive. In this group a relatively new device, Impella (Abiomed Cardiovascular, Inc, Danvers, MA) is notable for its minimally invasive, catheter-based cardiac assist device versions (LP 2.5 and LP 5 models) designed to unload the left ventricle with subsequent reduction of myocardial workload and oxygen consumption while increasing cardiac output,

coronary and end-organ perfusion. There are also surgically inserted versions to assist left ventricular (LD model) and right ventricular (RD model) functions. The miniaturized HeartWare MVAD (HeartWare, Inc., Massachusetts) is currently the smallest axial flow pump and is still in its preclinical development stage.

3-Third generation: These are mainly implantable centrifugal pumps developed for long-term use. Many devices in this group are newly developed or in development stage. Examples from this heterogeneous group are the DuraHeart (Terumo Heart, Inc., Michigan), VentrAssist (Ventracor, Australia), CorAide (Arrow International, Pennsylvania), HeartWare HVAD (HeartWare, Inc., Massachusetts) and Levacor (World Heart, Inc., Oakland, CA) systems. These pumps all use centrifugal energy to propulse blood but they somehow differ from each other in many aspects such as their implantation characteristics, dimensions, interrelation between the moving parts, working principles and device-blood interface. They have been subjected to vigorous animal, preclinical and clinical testing.

II - Total artificial hearts

The special indications for the use of these types of devices were summarized above (the indications for total artificial heart implantation). The implantation of these devices needs total cardiectomy, therefore, device explantation for any reason without impending heart transplantation is a problem. Initially two systems were granted by the Institute, namely the THI/Abiomed and Penn State/3M programs. The Sincardia CardioWest total artificial heart (CardioWest Technologies, Inc, Tucson, AZ) is developed from Jarvik 7-100, which was implanted to Barney Clark and was used in the early 1980s. It is the first FDA-approved device in its genre. It is a pneumatically driven (linked to an extracorporeal console), orthotopically implanted, biventricular, device that has been used extensively and successfully for bridging patients to transplantation in the past (23, 25, 42-44). In the US Food and Drug Administration Investigational Device Exemption study conducted in five US centers from 1993 to 2002 (23), hemodynamics were immediately improved by CardioWest TAH implantation. The mean support time was 79.1 days, and 79% of the implanted patients survived to transplantation. Survival to 1 year after transplantation was 85.9% (45). Strict anticoagulation is mandatory and the mobilization and rehabilitation of the patient is limited due to the external console. The Abiomed ABIOCOR (Abiomed Cardiovascular, Inc, Danvers,MA) is a newly developed completely self-contained heart replacement device. The system includes an intrathoracic pump, implantable battery, internal electronics and a wearable external battery pack delivering energy via abovementioned TETS unit. A centrifugal pump moves the hydraulic fluid between each ventricle component providing alternate left ventricular and right ventricular pulsatile flow. An atrial balance chamber makes adjustments for left and right atrial

pressures (16, 46, 47). Strict anticoagulation and antiplatelet treatment are mandatory. In 2001, ABIOCOR saw its first clinical application (47) and the FDA approved it for commercial approval under a Humanitarian Device Exemption in September, 2006. A new generation, smaller and durable model, AbioCor II is reported to be under development using ABIOMED and Penn State experiences.

III- External compression devices

It is not a new idea to support heart by external compression similar to the external cardiac massage during resuscitation (48). Among the main advantages is using natural interface between blood and pump (i.e. the patients own heart), obviating the use of anticoagulants while presumably reducing thromboembolic complications and blood-borne infections. External compression devices work by compressing the failing heart from its epicardial surface. The Anstadt cup in 1965 was a cardiac massage device used for cardiac arrest. Newer devices use a cuff or cup with an internal inflatable diaphragm, an electrocardiogram sensing trigger system and a driver console. The compression force generated by the device adds to the ventricular pressure generated by the native, contracting myocardium at the expense of some loss in diastolic compliance. This means higher filling pressures are needed to obtain the same preload (49, 50). Companies such as Cardio Technologies (Cardio Technologies , Inc., Pine Brook, NJ) and Abiomed (Heart Booster) (Abiomed Cardiovascular, Inc, Danvers, MA) have compression device development programs. Successful support for up to one week was reported in the previous animal studies (51). The insertion and weaning-off are expected to be easy and can be done without cardiopulmonary bypass. The device may also incorporate a weaning system using variable compression strength. Potential problems after prolonged use include rhythm disturbances and myocardial injury, ecchymosis and scarring caused by contusion and/or coronary compression (52). Among the cardiac assist concepts using external compression principle, the latissimus dorsi dynamic cardiomyoplasty is notable for using compressive force generated by patient's own, trained and synchronized skeletal muscle (53). In accordance with the results of many other centers, our institution's experience also demonstrated limited clinical success in a selected patient population (54-56). Currently, modifications of dynamic cardiomyoplasty using artificial muscle are under investigation (57).

Device implantation

Regardless of their generation, many LVAD systems use a left ventricle apical-connected inflow and an ascending aorta-connected a graft outflow. Total artificial hearts are orthotopically inserted. Depending on the device characteristics, the implantation can be under aortic cross-clamping, cardioplegic arrest, on cardiopulmonary bypass with the heart

beating, or without using extracorporeal circulation (off-pump). Bulky devices such as the first generation LVADs and total artificial hearts needs accurate sizing before implantation and there are three-dimensional computed tomography reconstruction models such as The Abiofit system developed for this purpose.

Device explantation

Except for a transplantation chance, the explantation of a LVAD may become mandatory due to-for example-device infection. There are anecdotal reports or observations demonstrating a sustained native left ventricular function adequate to support the circulation after the explantation. This may point out some recoverability in the left ventricular functions. However, in the long-term follow-up, many such patients died suddenly (even after 6 to 9 months), most probably due to fatal arrhythmias generated from the distended ventricle. On the other hand, patients surviving 2 years after the explantation were also reported. The LVAD application is thought to provide the failing heart with a resting period in which some recovery and reverse remodeling are possible. However, following the explantation, this healing process may stop and even be reversed (58). In addition, it is reported that the incidence of myocardial recovery after left ventricular assist device implantation in patients with chronic heart failure is low (59).

LVAD physiology

With total unloading the left ventricle, LVAD is added to the circulation in a serial manner. However, if there is some left ventricular reserve or residual volume in the left ventricle to open the aortic valve to generate a pulse, then the LVAD pump works in parallel with the native left ventricle. Therefore, both the device and the ventricle can pump blood into the ascending aorta. However, except during exercise, the aortic valve usually does not open. During the exercise, veins contract and venous return to the heart increases, causing an increase in common end-diastolic volume and the aortic valve opens indicating some contribution from the native ventricle. All LVADs are preload-dependent. Therefore, the combined output (LVAD+ventricle) can never exceed the output of right ventricle. Left ventricular assist devices need uncompromised filling from the right ventricle (ideally more than 3 lt/min./m² BSA). Therefore, especially during the first few days to weeks, any ischemia or sustained arrhythmia such as ventricular fibrillation should be avoided. After a few weeks, with the subsequent decrease in pulmonary vascular resistance, a loss in the right ventricular contribution mimicking a Fontan-type condition can be better tolerated.

Interventricular dependence: The right ventricle physically sits on the septum and a high-pressure chamber (left ventricle) and uses them as an anchorage. The LVADs, by effectively unloading the left ventricle, deprive the right ventricle from this physical support, causing interventricular septum to bulge leftward. This may worsen right ventricular dysfunction. On the other hand, left ventricular unloading causes some 15% decrease in pulmonary vascular resistance (pulmonary artery pressure may decrease by 30-40%) and venous return to the right ventricle increases. In addition, coronary perfusion to right ventricle improves. The sum of all these complex interactions determines the adequacy of LVAD filling.

Following assist device insertion, histological parameters such as myocyte damage regresses (60), reverse remodeling begins (61), and neurohormone levels decrease (62). Plasma volume decreases and excess fluid is extracted due to improvement in renal perfusion (63). The right and left atrial pressures drop and consequently, plasma rennin activity, aldosterone and vasopressin levels decline. Persistent high plasma renin activity is a poor prognostic sign and mortality predictor (63). Any incompetence of the aortic valve may cause a fatal condition creating a vicious-circle circulation (a variable part of the LVAD output repeatedly returns to the left ventricle to fill the LVAD again) and should be avoided at all cost, sometimes by oversewing the incompetent aortic valve. The device stopping in axial flow pumps also cause a potentially fatal condition mimicking massive aortic insufficiency.

Initial reports demonstrated very limited substantial increase in total body oxygen consumption (64) and modest improvements in exercise tolerance despite increased oxygen delivery and improved circulation provided by LVAD. This was attributed to chronic irreversible peripheral (for example intrinsic skeletal muscle and vasculature) changes (65, 66). However, newer reports are controversial, some demonstrating a good increase in oxygen uptake kinetics (67) total body oxygen consumption in LVAD recipients (68). In a recent study by Simon et al. (68), heart failure patients supported with a pneumatic LVAD are found to have better exercise tolerance than those receiving an electric LVAD. It is concluded that patients on LVAD support have better exercise tolerance than BiVAD-supported patients and it is thought that this highlights the importance of right ventricular function to exercise tolerance in heart failure patients (68).

LVAD immunobiology

More or less similar to cardiopulmonary bypass, any implanted mechanical assist device can trigger humoral and immunological cascades in the organism and puts the body in a procoagulant, proinflammatory, fibrinolytic and prothrombotic state (69). This is partly responsible for profuse bleeding complications shortly after LVAD insertion. The patients assisted by an LVAD are in a state of partial disseminated intravascular coagulation (DIC). Macrophage procoagulant activity is increased and many cascades and proinflammatory substances, including cytokines are activated (70). Anti-HLA antibodies are developed rapidly. While their level is approximately 4% in a patient with congestive heart failure, following LVAD insertion their level may increase to 47%. Panel

reactive antibody formation may jeopardize the success of a future transplantation (71). Anti-phospholipid antibodies also increase to a level about 43%, with a biphasic peak in coagulation cascade. The first peak is due to device implantation while the second is caused by immunocompetent cell lines colonizing the pseudointima lining the inside of the device. This surface, therefore starts to release substances sourced from dendritic components (Von Willebrand Factor, TM,CD34) and monocytic lines (CD68, CD14), that are selectively adhered to fibrin surface. Substances such as CD68, CD14, interleukin (IL)-1β, IL-2,6,8, tumor necrosis factor (TNF)α, tissue factor (TF), intercellular adhesion molecule (ICAM), vascular cell adhesion molecule (VCAM), E-selectin, CD2, 3, 25, are also released. On the other hand, in a susceptible patient population, the interaction between T-lymphocytes (CD2, 3, 25) and immunocompetent LVAD lining cells may cause B-cell (CD20) hyperactivity and autoimmunity. A sustained regression in CD4 T-lymphocyte population occurs due to apoptosis (72, 73). LVAD lining immunocompetent cells, or LVAD unloading of the failing heart may also contribute to the changes in nuclear transcription factor-KB (NF-KB) (74). Acetylsalicylic acid given 80 mg daily may prevent the activation of this factor and some other substances, inhibits CD68 macrophage activation, VCAM-1 expression, and untoward interactions between T and B-cells. Macrophage procoagulant activation is also inhibited and the formation of panel reactive antibodies is limited, which in turn greatly increases the success of a future transplantation.

A more recent study on TNFα, C3a, C5a, IL-6, and neutrophil elastase measurements in LVAD recipients revealed that IL-6 and C5a levels were increased significantly more in patients following implantation of an axial flow pump (MicroMed DeBakey) compared to the pulsatile Novacor device (75).

Perioperative patient care and problems

Bleeding: Both surgical and hematological causes and activated cascades described in the LVAD immunobiology section result in an increased oozing or active hemorrhage in the peri-implant period. In addition, preoperative liver compromise due to congestive heart failure may cause these patients to bleed profusely. In principle, all surgical bleeding sources, even the minor ones should be eliminated as much as possible before the chest closure. Bleeding will cause more bleeding due to dilution of coagulation factors (post transfusion coagulopathy) and release of cytokines and other substances. Even in the absence of blood donor shortage, bleeding means more transfusion, which ultimately increases pulmonary vascular resistance due to released vasoactive substances, right ventricle overload. This eventually means the failure of LVAD due to suboptimal filling. Aggressive transfusion also increases the formation of panel reactive antibodies, which substantially increase the risk of a future transplantation. To decrease the contact with donor-specific antigen, the blood should be filtered before being transfused.

Hypotension: Apart from hypovolemia or right ventricular dysfunction-related hypotension, a profound vasodilatation refractory to conventional vasopressors such as dopamine, may develop following device insertion and usually lasts for 24-36 hours. The main characteristics include a mean arterial pressure below 70 mmHg in the presence of a cardiac index over 2.5 L/min./m2, therefore it has similarities with septic shock, such as decreased vascular tonus. The exact mechanism of this phenomenon remains unknown but vasopressin deficiency, IL-1-dependent nitric oxide production, anti-natriuretic peptid, ATP-dependent K$^+$ channel activation with cGMP increase are among the possible explanations. Apart from usually being useless, many routinely-used vasopressors have untoward effects such as end-organ hypoperfusion, arrhythmias and tachyphylaxis development. If the patient is not responding to reasonable amounts of volume infusion, low doses of arginine vasopressin (0.04U/minute) is very efficient to restore vascular tonus (76).

Atrial fibrillation: Compromises right ventricle functions which in turn causes suboptimal LVAD filling. Anti arrhythmic drugs are used.

Ventricular arrhythmias: These compromise LVAD filling by abolishing effective right ventricular contractions. This complication may be well-tolerated a few weeks after the implantation, however in the early post-implant period may be fatal (see in the "LVAD physiology" section). Therefore, any sustained ventricular arrhythmia developed in the early postoperative period should be aggressively treated. There are reports of combined LVAD and cardioverter-defibrillator implantations in patients with retractable ventricular arrhythmias (77).

Antimicrobial prophylaxis: Strong anti-fungal and anti-staphylococcal prophylaxis is essential. An example is the "vancomycin+aztreonam+fluconazole" triple combination. Should any fungal infection develop, amphotericin often becomes necessary. The driveline exit port is a potential source of infection (37), therefore should be observed closely. In the early postoperative period, it is treated with chlorhexidine, and following wound healing, silverdine-containing ointments may be used for this purpose. All intravascular catheters and lines should be withdrawn as soon as possible. Infection following LVAD insertion is observed in about 30-50%, carrying some 20-70% mortality. In addition, a persistent infection may preclude future transplantation opportunity in approximately 20% of infected LVAD recipients. Vegetations lodged on LVAD prosthetic valves may also cause thromboembolism. The most frequently responsible microorganisms are Staphylococcus epidermidis and Candida albicans, causing a bacteriemia/fungemia manifesting one month after the implantation, a condition that mandates device explantation and a subsequent high-risk transplantation (78).

Low cardiac output: In about 90% of the cases, the reason is right ventricular failure, usually related to profuse bleeding with subsequent massive transfusion, right ventricular ischemia, or ventricular arrhythmias, etc. The patient should leave the operation room without volume deficiency. Any arrhythmia should be promptly terminated. Hypothermia increases bleeding and pulmonary vascular resistance,

therefore, should be avoided. Early extubation improves the right ventricular dynamics by restoring autonomic compensation mechanisms, and therefore, is desired.

Sudden LVAD filling compromise: Cannula obstructions and kinked lines may impair device functions. The inflow cannula obstruction can be seen on bedside echocardiography with a distended left ventricle. In the long-term follow-up, the possible causes include prosthetic inflow valve thrombosis or infection, suction of ventricular wall into the device, right ventricular dysfunction, kinked lines, etc.

Persistent hypoxia: A patent foramen ovale may be the cause and can be detected on echocardiography. Pulmonary causes should be excluded. The ECMO is not proven beneficial in such conditions.

Thrombocytopenia: Platelet number decreases rapidly in the first hours/days due to aggregation and adherence to the device interior surface.

Abdominal discomfort: It occurs frequently with the older-type bulky devices positioned intraabdominally or preperitoneally. Frequent but small meals are given. Sometimes abdominal pain and discomfort may be the early sign of a developing infection in the LVAD pocket.

Hemodialysis: Preimplant renal function impairment may dictate the liberal and early use of hemodialysis (CVVHF or CAVH) in assist device recipients (79) with or without using a right ventricle-supporting device.

Hypertension: Any hypertensive tendency masked by the existing heart failure may become manifest with the establishment of near normal output supplied by the LVAD. Usually a pure vasodilator is preferred in the management. Beta-blocking agents or calcium antagonists are often avoided.

Thromboembolism and stroke: The incidence greatly varies with the type of the device. The HeartMate device enjoys a relatively low incidence of thromboembolic events (2-4%/per patient year) despite no anticoagulation due to its specially designed interior surface (35). However, stroke incidences may exceed 25-50% in other devices (29). Microembolizations and subclinical neurological events need further long-term neurocognitive tests and detailed studies (80).

Right ventricular failure: Clinically overt right ventricular failure becomes manifest in 20% of the LVAD recipients. The possible causes have been previously discussed. Briefly, the underlying cardiomyopathy, air embolism, prolonged right ventricular distention, poor myocardial protection, damage to the present coronary grafts, right ventricular ischemia due to coronary artery disease, total unloading of left ventricle with LVAD (impaired ventricular interdependence; see above), chest closure at the termination of the operation (this may reduce output by 300 ml), and above all, bleeding and subsequent transfusion in association with vasoactive substance release (C5a, Thromboxane A2) are among the major causes. Regardless of cause, the diagnosis of right ventricular failure should not be delayed. A central venous pressure exceeding 20 mmHg, giant v-waves, a left atrial pressure less than 10 mmHg, a cardiac index less than 1.8 lt/min/m^2 BSA, a distended right ventricle, septal shift and massive tricuspid regurgitation at bedside echocardiography, support the diagnosis. Inhaled nitric oxide may help resolve any pulmonary resistance related compromise (81). Regardless of a cause, approximately 10% of the cases need some sort of right ventricular mechanical support (RVAD). A relatively simple and efficient way to decompress the right ventricle is to create a controlled, centrifugal pump-driven peripheral veno-arterial shunt without an oxygenator in the circuit. At relatively low flow rates of 1-1.25 L/min., this peripheral (jugular vein to femoral artery) right-to-left shunt, decompresses right ventricle, improves systemic cardiac output at tolerable oxygen saturations. It is usually used for 6-12 hours and does not require systemic heparinization. Due to peripherally located inflow and outflow cannulation, oxygen-rich blood from the native left ventricle mainly goes toward brain and kidneys. This peripheral shunt is also reported to have both physiologic and technical advantages over a central shunt (82). The last resort in severe, retractable right ventricle failure is to insert a right ventricular assist device (RVAD). Once the use of a RVAD is deemed unavoidable, there should be no further delay. The early insertion of a RVAD, may improve survival about 55% in this mortal situation. The right ventricle is usually supported for about 5 days. The chest is often left open, and heparin is not given until the chest drainage subsides. The addition of a hemodialysis device to the RVAD circuit is often beneficial in these circumstances (79). The ABIOMED BVS 5000, or sometimes short-term centrifugal pumps such as BIOMEDICUS are used for right ventricular assistance.

Mechanical complications: Device malfunction, inflow conduit rupture and lead break are mechanical complications. These may fatally end, therefore prompt replacement of the problematic component or the whole device becomes mandatory (83).

Rehabilitation of the assist device patient

Early and progressive ambulation and return to daily life is essential for any patient undergoing an assist device insertion (84). It is important to encourage patients to control activities of daily living. The attainment of effective circulatory support provides an opportunity for aggressive physical rehabilitation, which is of paramount importance in converting the wasted and bed-bound end-stage heart failure patient into an ambulating reconditioned heart transplant candidate (85). The rehabilitation begins in the first postoperative day in the intensive care unit. There are certain stages of the rehabilitation process:

Stage-1: The Goal: To avoid complications of being bed-bound. The Tool: Chest and pulmonary exercises, Range of motion exercises (ROM), positioning, sitting on a chair. The Period: As soon as hemodynamic stability is accomplished (days 2-7). The Place: The Intensive Care Unit (the average ICU stay is about 8±5 days).

Stage-2: The Goal: To decrease dependency on others in daily activities. The Tool: Ambulation. The Period: Between the first and second postoperative weeks. The Place: The postoperative ward.

Stage-3: The Goal: To gain condition and physical fitness. The Tool: Treadmill and bicycle exercises. The Period: After the second postoperative week, until sternal union is completed (6-8 weeks). The Place: The exercise saloon.

Stage-4: The Goal: To gain strength; increasing muscle tonus, power and mass. The optimization of nutrition before a future transplantation. The Tool: Resistance exercises. The Period: After the completion of sternal union (from the 6th or 8th weeks). The Place: The fitness saloon.

Stage-5: The Goal: To gain self-confidence, returning to daily life, social and psychological adaptation. The Tool: Daily activities, walking, bicycle riding, dancing. The Period: After discharge and sternal union (heavy activities are not recommended for 3 months). The Place: At home, daily environment (shower caps and holsters are provided, jumping and diving are not allowed).

The criteria for terminating a physical therapy session include any subjective intolerance, a significant drop of assist device flow, hypotension associated with fainting, dizziness, or diaphoresis, severe, intolerable dyspnea, a saturation less than 90% on supplemental oxygen, significant chest pain or discomfort, extreme fatigue, request of patient to stop (86).

Cost of assist device applications

With the increasing clinical use and success of left ventricular assist devices, there is a growing need to assess the cost efficacy of the devices to determine the value of this treatment modality. Due to the amazing differences in cost-determining variables such as the device type, different pricing for countries or institutions, length of hospital stays, rehospitalization rates, complication profiles, care costs, it is nearly impossible to determine constant price for device applications. However, there are still attempts to determine an average cost of the procedure and to compare it to those of other treatment modalities. In a study by DiGiorgi et al. (87) from the United States, left ventricular assist device implantation has been found to be associated with longer length of stay and higher cost for initial hospitalization compared with orthotopic heart transplantation. In this report, total actual hospital costs after LVAD insertion averaged 197.957±77.291 U.S. dollars and the assist device patients are found to have higher re-admission rates compared with orthotopic heart transplantation but similar costs and length of stay. It is concluded that reimbursements for LVAD therapy are relatively low, resulting in significant lost revenue and, if LVAD therapy is to become a viable alternative, improvements in both cost-effectiveness and reimbursement will be necessary (87).

Long-term results and quality of life

There are many studies attempting to analyze long-term clinical success of assist device applications in terms of survival, hemodynamic and clinical parameters and quality of life indices.

Again, there are many variables, such as device type (pulsatile LVADs, axial flow pumps, total artificial hearts), observation duration (long- or short- term) and initial indication of device use (BTR; BTT; DT), making any comparison difficult. The most important long term study is the REMATCH (Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure) study (12), indicating a reduction of 48% in the death risk by any cause in the group that received LVADs as compared with the medical-therapy. The rates of survival at one year were 52% in the device group and 25% in the medical-therapy group (p=0.002), and the rates at two years were 23% and 8% (p=0.09), respectively. Despite the substantial survival benefit, the morbidity and mortality associated with the use of the LVAD were considerable. In particular, infection, bleeding and mechanical failure of the device were major factors in the two-year survival rate of only 23 percent. Investigators found that malnutrition was a problem in these patients, which predisposed them to infection and other complications.

Mechanical, histological, and biochemical improvements have been described in patients after LVAD support. Explantation of the LVADs without heart transplantation has been described in selected patients who received this therapy as a bridge to transplantation. A prospective multicenter study attempted to identify potential explantation candidates by the use of exercise testing (59). Significant myocardial recovery after LVAD therapy in patients with end-stage congestive heart failure occurred in a small percentage of patients in this study. In another study assessing hemodynamic parameters such as left ventricular indices, cardiac function improved significantly after device implantation, but although cellular recovery and improvement in ventricular function are observed, the degree of clinical recovery was found to be insufficient for device explantation in most patients with chronic heart failure (66). Many of similar studies were done on patients with first-generation pulsatile devices such as HeartMate but other reports concerning with axial flow pumps are also available. In the study of Siegenthaler et al. (40), it is concluded that continuous flow blood pumps provided symptomatic relief of severe heart failure with high quality of life, with an event-free survival reaching 4 years.

There are also studies analyzing quality of life in LVAD recipients. In a longitudinal, multi-site study compares quality of life outcomes of patients listed for heart transplantation that required a LVAD. The assessment was made at 3 months after implantation of an LVAD vs. 3 months after heart transplantation. Patients were significantly more satisfied with their lives overall and with their health and functioning at 3 months after heart transplantation as compared with 3 months after LVAD implantation. Mobility, self-care ability, physical ability and overall functional ability improved from 3 months after LVAD implant to 3 months after heart transplant. There was significantly less symptom distress after LVAD implant as compared with after heart transplant for the neurological, dermatologic and physical sub-scales. Work/school/financial stress was significantly lower after heart transplant vs. after LVAD implant. In contrast, 2 other areas of stress were significantly lower after LVAD implant vs. after heart transplant: self-care stress and hospital/clinic-related stress (88).

In another recent study, longer term quality of life outcome in patients who have had a LVAD for bridge to recovery explanted due to myocardial recovery (BTR: an average of 3.6±1.9 years since LVAD removal) was assessed and compared to bridge-to-transplant (BTT: an average of 3.3±2.3 years since transplantation) and transplanted (Tx: an average of 3.8±0.6 years since transplantation) patients (89). Quality of life Short Form-36 (SF-36) questionnaires were significantly better in the BTR group compared with the BTT and Tx groups. Analysis of the two main dimensions and the total SF-36 score between the three groups showed that: 1) physical health dimension tended to be better in BTR vs. BTT and Tx groups (p>0.05); 2i) mental health dimension was better in both BTR and BTT groups compared with the Tx group (p<0.05); and 3) total SF-36 score was significantly higher in the BTR and BTT groups compared with the Tx group. It is concluded that the BTR patients appear to have better quality of life than both BTT and Tx patients. In addition, BTT patients seem to have a better quality of life compared with Tx patients, suggesting that placement of ventricular assist devices could improve the physiologic outcome for transplanted patients (89).

In another study by a European center, the differences in quality of life and psychological adjustment for current LVAD patients, were assessed in a sample consisting of patients who have been transplanted a LVAD and patients in whom the device has been explanted. Although there were no significant differences between the three groups, there was a trend for the LVAD patients to have higher levels of anxiety and depression and a lower quality of life compared with transplanted or explanted patients (90). It was concluded that psychological assessment and interventions to reduce psychological morbidity and improve quality of life would be important in these patients, particularly in view of the increasing numbers of LVADs being implanted and the possibility of their use for long-term "destination" therapy.

Recovery in the organ functions

Mechanical device support improves hemodynamics and end-organ perfusion in critically ill patients. This may stop, even reverse the damaging effects of end-stage heart disease on the organs and allows for recovery of the organ functions (91). This beneficial effect may be partly responsible for better results after transplantation in LVAD recipients in comparison to those undergoing transplantation without prior bridging with mechanical assist devices (92). It often takes at least 4-5 weeks for hepatic and renal functions to recover after assist device insertion. This implies that a relatively prolonged support is necessary for organ recovery (93).

Mechanical circulatory support device database of the International Society for Heart and Lung Transplantation

During its first 3 years, this database has collected data on more than 655 device implants from 60 centers around the world, roughly 67% of them in the USA (2). According to the "Mechanical Circulatory Support Device Database of the International Society for Heart and Lung Transplantation: Third Annual Report-2005", among the 655 patients, the device used in the majority of patients was the isolated LVAD. Of the 542 LVADs placed, nearly 90% were long-term pulsatile flow devices. Despite an evolving interest in mechanical circulatory support as permanent destination therapy for advanced heart failure, nearly 80% of devices were placed with the intent of bridging to transplantation, whereas only about 12% were placed as destination devices.

Overall survival: The actuarial survival during device support was 83% at 1 month and 50% at 1 year. The death risk was highest during the first month after implantation. The major causes of perioperative death were multi-organ failure and bleeding complications. The need for biventricular support and older patient age were the major risk factors for early mortality.

Long-term follow-up according to indication groups: Infection continued to be the major complication limiting outcomes in the first year.

Bridge to transplantation: Here the recipient age influenced the success of bridging significantly. It was observed that, in patients older than 50 years of age, approximately 50% of patients received a heart transplant by 1 year, but nearly 40% died during VAD support. On the other hand, for patients <30 years of age, bridging has been extremely successful. Nearly 75% of these patients were transplanted by 1 year and only 13% died while on ventricular assist device support.

Bridge to recovery: The number of patients who have been successfully weaned from device support has remained small. Only 35 such patients were identified in the database, representing about 5% of the overall experience. A higher proportion of these patients received biventricular support compared with the overall VAD population. The vast majority of patients who underwent device explantation had been supported for <3 months.

Destination therapy: Destination therapy is receiving intense scrutiny as the experience evolves around the world. Seventy-eight such patients were identified in the registry. The vast majority are triaged to destination therapy because of advanced age or severe co-morbidities, which make them poorly suited for transplantation. As expected, most of these patients received pulsatile LVADs. Among the entire cohort of destination patients, the actual survival was 65% at 6 months and 34% at 1 year. Older age remained a major risk factor for mortality. Among patients <65 years of age at the time of destination therapy, the actual survival at 1 year was 41% vs. 26% for those over the age of 65 years.

Conclusion

Since the commencement of the artificial-heart program at the National Institutes of Health in 1964, many circulatory-support devices have been developed for short-term use in patients with end-stage heart failure. In 1994, the Food and

Drug Administration approved pneumatically driven left ventricular assist devices as a bridge to transplantation, and self-contained, vented electric devices were approved for this purpose in 1998. Bridge to transplantation is particularly successful in younger adults, successful bridging occurring in nearly 75% of cases. When devices are placed for bridging to recovery, device explantation is possible in about 45% of patients. The use of mechanical support devices for destination therapy is still under vigorous investigation but this type of use still represents only 12% of cases. One-year survival among destination patients is 34%, but improves to 40% for those patients younger than 65 years of age. Nevertheless, VADs will be a major topic of interest in the following decades.

Grant support

References

1. Taylor DO, Edwards LB, Aurora P, Christie JD, Dobbels F, Kirk R, et al. Registry of the International Society for Heart and Lung Transplantation: twenty-fifth official adult heart transplant report-2008. J Heart Lung Transplant 2008; 27: 943-56.
2. Deng MC, Edwards LB, Hertz MI, Rowe AW, Keck BM, Kormos R, et al. International Society for Heart and Lung Transplantation. Mechanical circulatory support device database of the International Society for Heart and Lung Transplantation: third annual report-2005. J Heart Lung Transplant 2005; 24:1182-7.
3. Hall CW, Liotta D, Henly WS, Crawford ES, DeBakey ME. Development of artificial intrathoracic circulatory pumps. Am J Surg 1964; 108: 685-92.
4. DeBakey ME. Left ventricular bypass pump for cardiac assistance. Clinical experience. Am J Cardiol 1971; 27:3-11.
5. Department of Health and Human Services, National Institutes for Health, National Heart, Lung and Blood Institute. Request for proposal. Left heart assist blood pumps. Bethesda, MD: NIH.1977.
6. Department of Health and Human Services, National Institutes for Health, National Heart, Lung and Blood Institute. Request for proposal. Development of electrical energy converters to power and control left heart assist devices. Bethesda, MD: NIH.1977.
7. Cooley DA, Liotta D, Hallman GL, Bloodwell RD, Leachman RD, Milam JD. Orthotopic cardiac prosthesis for two-staged cardiac replacement. Am J Cardiol 1969; 24: 723-30.
8. Norman JC, Brook MI, Cooley DA, Klima T, Kahan BD, Frazier OH, et al. Total support of the circulation of a patient with post-cardiotomy stone-heart syndrome by a partial artificial heart (ALVAD) for 5 days followed by heart and kidney transplantation. Lancet 1978; 1:1125-7.
9. Frazier OH. The development of an implantable, portable, electrically powered left ventricular assist device. Semin Thorac Cardiovasc Surg 1994; 6: 181-7.
10. Department of Health and Human Services, National Institutes for Health, National Heart, Lung and Blood Institute. Request for proposal. Innovative ventricular assist systems Bethesda, MD: NIH.1994.
11. Helman DN, Maybaum SW, Morales DL, Williams MR, Beniaminovitz A, Edwards NM, et al. Recurrent remodeling after ventricular assistance: Is long-term myocardial recovery attainable? Ann Thorac Surg 2000; 70: 1255-8.
12. Rose EA, Gelijns AC, Moskowitz AJ, Heitjan DF, Stevenson LW, Dembitsky W, et al; Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) Study Group. Long-term mechanical left ventricular assistance for end-stage heart failure. N Engl J Med 2001; 345: 1435-43.
13. Akalın H, Corapcioglu ET, Ucanok K, Eren NT, Aral A, Ozyurda U, et al. The first artificial heart application in our country (Symbion J-7). Türkiye Klinikleri 1989; 9: 294-6.
14. Vural K, Tasdemir O, Kucukaksu S, Tarcan O, Kucuker S, Sener E. Long-term results of latissimus dorsi dynamic cardiomyoplasti operations. Turkish Journal of Thoracic and Cardiovascular Surgery 2001; 9:15-20.
15. Pennington DG, Swartz MT. Patient selection for mechanical circulatory support. In: Ott RA, Gutfinger DE, Gazzaniga AB, editors. Cardiac Surgery: State of the Art Reviews: Mechanical Cardiac Assist. Philadelphia: Hanley and Belfus, Inc.; 1993. p.229-39.
16. DiGiorgi PL, Rao V, Naka Y, Oz MC. Which patient, which pump? J Heart Lung Transplant 2003; 22: 221-35.
17. DeRose JJ Jr, Umana JP, Argenziano M, Catanese KA, Levin HR, Sun BC, et al. Improved results for postcardiotomy cardiogenic shock with the use of implantable left ventricular assist devices. Ann Thorac Surg 1997; 64: 1757-63.
18. Smalling RW. The use of mechanical assist devices in the management of cardiogenic shock secondary to acute myocardial infarction. Texas Heart Inst J 1991; 18: 275-81.
19. Koul B, Solem JO, Steen S, Casimir-Ahn H, Granfeldt H, Lönn UJ. HeartMate left ventricular assist device as bridge to heart transplantation. Ann Thorac Surg 1998; 65: 1625-30.
20. Chillcott SR, Atkins P J, Adamson RM. Left ventricular assist as a viable alternative for cardiac transplantation. Crit Care Nurs Q 1998; 20: 64-79.
21. McCarthy PM, Young JB, Smedira NG, Hobbs RE, Vargo RL, Starling RC. Permanent mechanical circulatory support with an implantable left ventricular assist device. Ann Thorac Surg 1997; 63: 1458-61.
22. Piccione W Jr. Mechanical circulatory assistance: Changing indications and options. J Heart Lung Transplant 1997; 16: 25-8.
23. Copeland JG, Smith RG, Arabia FA, Nolan PE, Sethi GK, Tsau PH, et al; CardioWest Total Artificial Heart Investigators. Cardiac replacement with a total artificial heart as a bridge to transplantation. N Engl J Med 2004; 351: 859-67.
24. De Vries WC, Anderson JL, Joyce LD, Anderson FL, Hammond EH, Jarvik RK, et al. Clinical use of the total artificial heart. N Engl J Med 1984; 310:273-8.
25. Copeland JG, Arabia FA, Smith R, Nolan P. The CardioWest total artificial heart. In: Goldstein DJ, Oz MC, editors. Cardiac Assist Devices. Armonk, NY: Futura; 2000. p.341-55.
26. Dowling RD, Gray LA Jr, Etoch SW, Laks H, Marelli D, Samuels L, et al. Initial experience with the AbioCor implantable replacement heart system. J Thorac Cardiovasc Surg. 2004; 127: 131-41.
27. Mielniczuk L, Mussivand T, Davies R, Mesana TG, Masters RG, Hendry PJ, et al. Patient selection for left ventricular assist devices. Artif Organs 2004; 28: 152-7.
28. Oz MC, Rose EA, Levin HR. Selection criteria for placement of left ventricular assist devices. Am Heart J 1995; 129: 173-7.
29. Ramasamy N, Vargo RL, Kormos RL, Portner PM. The Novacor left ventricular assist system. In: Goldstein DJ, Oz MC, editors. Cardiac Assist Devices. Armonk, NY: Futura; 2000. p.323-40.
30. Goldstein DJ. Thermo Cardiosystems ventricular assist devices. In: Goldstein DJ, Oz MC, editors. Cardiac Assist Devices. Armonk, NY: Futura; 2000. p.307-21.

31. Ochiai Y, McCarthy PM, Smedira NG, Banbury MK, Navia JL, Feng J, et al. Predictors of severe right ventricular failure after implantable left ventricular assist device insertion: analysis of 245 patients. Circulation 2002; 106(12 Suppl 1): I198-202.

32. Sun BC. Indications for long-term assist device placement as a bridge to transplantation. Cardiol Clinics 2003; 21: 51-5.

33. Aaronson KD, Patel H, Pagani FD. Patient selection for left ventricular assist device therapy. Ann Thorac Surg 2003; 75: S29-35.

34. El-Banayosy A, Arusoglu L, Kizner L, Tenderich G, Minami K, Inoue K, et al. Novacor left ventricular assist system versus Heartmate vented electric left ventricular assist system as a long-term mechanical circulatory support device in bridging patients: a prospective study. J Thorac Cardiovasc Surg 2000; 119: 581-7.

35. Slater JP, Rose EA, Levin HR, Frazier OH, Roberts JK, Weinberg AD, et al. Low thromboembolic risk without anticoagulation using advanced-design left ventricular assist devices. Ann Thorac Surg 1996; 62: 1321-7.

36. Lee J, Miller PJ, Chen H, Conley MG, Carpenter JL, Wihera JC, et al. Reliability model from the in vitro durability tests of a left ventricular assist system. ASAIO J 1999; 45: 595 -601.

37. Zierer A, Melby SJ, Voeller RK, Guthrie TJ, Ewald GA, Shelton K, et al. Late-onset driveline infections: the Achilles' heel of prolonged left ventricular assist device support. Ann Thorac Surg 2007; 84: 515-20.

38. Nosé Y. Design and development strategy for the rotary blood pump. Artif Organs 1998; 22: 438-46.

39. Zhang Y, Zhan Z, Gui XM, Sun HS, Zhang H, Zheng Z, et al. Design optimization of an axial blood pump with computational fluid dynamics. ASAIO J. 2008; 54:150-5.

40. Siegenthaler MP, Westaby S, Frazier OH, Martin J, Banning A, Robson D, et al. Advanced heart failure: feasibility study of long-term continuous axial flow pump support. Eur Heart J 2005; 26:1031-8.

41. Wakisaka Y, Taenaka Y, Chikanari K, Nakatani T, Tatsumi E, Masuzawa T, et al. Long-term evaluation of a nonpulsatile mechanical circulatory support system. Artif Org 1997; 21: 639-44.

42. Copeland JG, Pavie A, Duveau D, Keon WJ, Masters R, Pifarre R, et al. Bridge to transplantation with the CardioWest total artificial heart: The international experience 1993 to 1995. J Heart Lung Transplant 1996; 15: 94-9.

43. Arabia FA, Copeland JG, Smith RG, Sethi GK, Arzouman DA, Pavie A, et al. International experience with the CardioWest total artificial heart as a bridge to heart transplantation. Eur J Cardiothorac Surg 1997; 11(suppl): S5-10.

44. Copeland JG, Arabia FA, Banchy ME, Sethi GK, Foy B, Long J, et al. The CardioWest total artificial heart bridge to transplantation: 1993 to 1996 national trial. Ann Thorac Surg 1998; 66: 1662-9.

45. Copeland JG, Smith RG, Bose RK, Tsau PH, Nolan PE, Slepian MJ. Risk factor analysis for bridge to transplantation with the CardioWest total artificial heart. Ann Thorac Surg. 2008; 85: 1639-44.

46. Samuels L. The AbioCor totally implantable replacement heart. Am Heart Hosp J 2003; 1: 91-6.

47. SoRelle R. Cardiovascular news. Totally contained Abio-Cor artificial heart implanted July 3, 2001. Circulation 2001; 104: E9005-6.

48. Anstadt GL, Blakemore WS, Baue AE. A new instrument for prolonged mechanical massage. Circulation 1965; 31(suppl II): 43.

49. Artrip JH, Yi GH, Shimizo J, Feihn E, Sciacca RR, Wang J, Burkhoff D. Maximizing hemodynamic effectiveness of biventricular assistance by direct cardiac compression studied in ex vivo and in vivo canine models of acute heart failure. J Thorac Cardiovasc Surg 2000; 120: 379-86.

50. Artrip JH, Yi GH, Levin HR, Burkhoff D, Wang J. Physiological and hemodynamic evaluation of nonuniform direct cardiac compression. Circulation 1999; 100: II 236-43.

51. Perez-Tamayo RA, Anstadt MP, Cothran RL, Reisinger RJ, Schenkman DI, Hulette C, et al. Prolonged total circulatory support using direct mechanical ventricular actuation. ASAIO J 1995; 41: M512-7.

52. Anstadt MP, Perez-Tamayo RA, Banit DM, Walthall HP, Cothran RL, Abdel-Aleem S, et al. Myocardial tolerance to mechanical actuation is affected by biomaterial characteristics. ASAIO J 1994; 40: M329-34.

53. Chachques JC, Carpentier AF. The scientific development of dynamic cardiomyoplasty. J Thorac Cardiovasc Surg. 1995; 110 (4 Pt 1):1154-5.

54. Tasdemir O, Vural KM, Kucukaksu SD, Tarcan OK, Ozdemir M, Kutuk E, et al. Comparative study on cardiomyoplasty patients with the cardiomyostimulator on versus off. Ann Thorac Surg 1996; 62:1708-13.

55. Tasdemir O, Kucukaksu SD, Vural KM, Katircioglu FS, Kutuk E, Bayazit K. A comparison of the early and midterm results after dynamic cardiomyoplasty in patients with ischemic or idiopathic cardiomyopathy. J Thorac Cardiovasc Surg 1997; 113: 173-80.

56. Vural K, Tasdemir O, Kucukaksu S, Tarcan O, Kucuker S, Sener E. Latissimus dorsi dinamik kardiyomiyoplasti ameliyatlarının uzun dönem sonuçları. Türk Göğüs Kalp Damar Cerrahisi Dergisi 2001; 9: 15-20.

57. Suzuki Y, Daitoku K, Minakawa M, Fukui K, Fukuda I. Dynamic cardiomyoplasty using artificial muscle. J Artif Organs 2008; 11:160-2.

58. Frazier OH, Benedict CR, Radovancevic B, Bick RJ, Capek P, Springer WE, et al. Improved left ventricular function after chronic left ventricular unloading. Ann Thorac Surg 1996; 62: 675-82.

59. Mancini DM, Beniaminovitz A, Levin H, Catanese K, Flannery M, DiTullio M, et al. Low incidence of myocardial recovery after left ventricular assist device implantation in patients with chronic heart failure. Circulation 1998; 98: 2383-9.

60. McCarthy PM, Nakatani S, Vargo R, Kottke-Marchant K, Harasaki H, James KB, et al. Structural and left ventricular histologic changes after implantable LVAD insertion. Ann Thorac Surg 1995; 59: 609-13.

61. Zafeiridis A, Jeevanandam V, Houser S, Margulies K. Regression of cellular hypertrophy after left ventricular assist device support. Circulation 1998; 98: 656-62.

62. James KB, McCarthy PM, Thomas JD, Vargo R, Hobbs RE, Sapp S, et al. The effect of left ventricular assist device on neuroendocrine activation in heart failure. Circulation 1995; 92: 191-5.

63. James KB, McCarthy PM, Jaalouk S, Bravo EL, Betkowski A, Thomas JD, et al. Plasma volume and its regulatory factors in congestive heart failure after implantation of long-term left ventricular assist devices. Circulation 1996; 93: 1515-9.

64. Mancini D, Goldsmith R, Levin H, Beniaminovitz A, Rose E, Catanese K, et al. Comparison of exercise performance in patients with chronic severe heart failure versus left ventricular assist devices. Circulation. 1998; 98: 1178-83.

65. Mancini D, Beniaminowitz A. Exercise performance in patients with left ventricular assist devices. In: Goldstein DJ, Oz MC, editors. Cardiac Assist Devices. Armonk, NY: Futura; 2000. p.137-52.

66. Maybaum S, Mancini D, Xydas S, Starling RC, Aaronson K, Pagani FD, et al; LVAD Working Group. Cardiac improvement during mechanical circulatory support: a prospective multicenter study of the LVAD Working Group. Circulation. 2007; 115: 2497-505.

67. Feldman CM, Khan SN, Slaughter MS, Sobieski M, Graham JD, Eaheart B, et al. Improvement in early oxygen uptake kinetics with left ventricular assist device support. ASAIO J 2008; 54: 406-11.

68. Simon MA, Kormos RL, Gorcsan J 3rd, Dohi K, Winowich S, Stanford E, et al. Differential exercise performance on ventricular assist device support. J Heart Lung Transplant 2005; 24:1506-12.

69. Spanier T, Oz M, Levin H, Weinberg A, Stamatis K, Stern D, et al. Activation of coagulation and fibrinolytic pathways in patients with left ventricular assist devices. J Thorac Cardiovasc Surg 1996; 112:1090-7.
70. Corry DC, DeLucia A 3rd, Zhu H, Radcliffe RR, Brevetti GR, El-Khatib H, et al. Time course of cytokine release and complement activation after implantation of the HeartMate left ventricular assist device. ASAIO J 1998; 44: M347-51.
71. Massad MG, Cook DJ, Schmitt SK, Smedira NG, McCarthy JF, Vargo RL, et al. Factors influencing HLA sensitization in implantable LVAD recipients. Ann Thorac Surg 1997; 64: 1120-5.
72. Ankersmit HJ, Edwards NM, Schuster M, John R, Kocher A, Rose EA, et al. Quantitative changes in T-cell populations after left ventricular assist device implantation: relationship to T-cell apoptosis and soluble CD95. Circulation 1999; 100 (19 Suppl): II211-5.
73. Ankersmit HJ, Tugulea S, Spanier T, Weinberg AD, Artrip JH, Burke EM, et al. Activation-induced T-cell death and immune dysfunction after implantation of left-ventricular assist device. Lancet 1999; 354: 550-5.
74. Grabellus F, Levkau B, Sokoll A, Welp H, Schmid C, Deng MC, et al. Reversible activation of nuclear factor-kappaB in human end-stage heart failure after left ventricular mechanical support. Cardiovasc Res 2002; 53: 124-30.
75. Loebe M, Koster A, Sänger S, Potapov EV, Kuppe H, Noon GP, et al. Inflammatory response after implantation of a left ventricular assist device: comparison between the axial flow MicroMed DeBakey VAD and the pulsatile Novacor device. ASAIO Journal 2001; 47: 272-4.
76. Argenziano M, Choudhri AF, Oz MC, Rose EA, Smith CR, Landry DW. A prospective randomized trial of arginine vasopressin in the treatment of vasodilatory shock after left ventricular assist device placement. Circulation 1997; 96(9 Suppl): II-286-90.
77. Deng MC, Tjan TD, Asfour B, Gradaus R, Böcker D, Loick HM, et al. Combining nonpharmacologic therapies for advanced heart failure: the Münster experience with the assist device-defibrillator combination. Am J Cardiol 1999; 83(Suppl 5B): 158D-160D.
78. Fischer SA, Trenholme GM, Costanzo MR, Piccione W. Infectious complications in left ventricular assist device recipients. Clinical Infectious Diseases CID 1997; 24: 18-23.
79. Chen JM, Levin HR, Catanese KA, Sistino JJ, Landry DW, Rose EA, et al. Use of a pulsatile right ventricular assist device and continuous arteriovenous hemodialysis in a 57-year-old man with a pulsatile left ventricular assist device. J Heart Lung Transplant 1995;14 (1 Pt 1): 186-91.
80. Moazami N, Roberts K, Argenziano M, Catanese K, Mohr JP, Rose EA, et al. Asymptomatic microembolism in patients with long-term ventricular assist support. ASAIO J 1997; 43: 177-80.
81. Hare JM, Shernan SK, Body SC, Graydon E, Colucci WS, Couper GS. Influence of inhaled nitric oxide on systemic flow and ventricular filling pressure in patients receiving mechanical circulatory assistance. Circulation 1997; 95: 2250-3.
82. Slater JP, Goldstein DJ, Ashton RC Jr, Levin HR, Spotnitz HM, Oz MC. Right-to-left veno-arterial shunting for right-sided circulatory failure. Ann Thorac Surg 1995; 60: 978-85.
83. Scheld HH, Soepanvata R, Schmid C, Loick M, Weyand M, Hammel D. Rupture of inflow conduits in the TCI-Heart Mate system. J Thorac Cardiovasc Surg 1997; 114: 287-9.
84. Morrone TM, Buck LA, Catanese KA, Goldsmith RL, Cahalin LP, Oz MC, et al. Early progressive mobilization of patients with left ventricular assist devices is safe and optimizes recovery before heart transplantation. J Heart Lung Transplant 1996; 15: 423-9.
85. Morrone TM, Buck LA. Rehabilitation of the ventricular assist device recipient. In: Goldstein DJ, Oz MC, editors. Cardiac Assist Devices. Armonk, NY: Futura, 2000, p.167-76.
86. Perme CS, Southard RE, Joyce DL, Noon GP, Loebe M. Early mobilization of LVAD recipients who require prolonged mechanical ventilation. Tex Heart Inst J 2006; 33: 130-3.
87. DiGiorgi PL, Reel MS, Thornton B, Burton E, Naka Y, Oz MC. Heart Transplant and Left Ventricular Assist Device Costs. J Heart Lung Transplant 2005;24: 200-4.
88. Grady KL, Meyer PM, Dressler D, White-Williams C, Kaan A, Mattea A, et al. Change in quality of life from after left ventricular assist device implantation to after heart transplantation. J Heart Lung Transplant 2003; 22:1254-67.
89. George RS, Yacoub MH, Bowles CT, Hipkin M, Rogers P, Hallas C, et al. Quality of life after removal of left ventricular assist device for myocardial recovery. J Heart Lung Transplant 2008; 27:165-72.
90. Wray J, Hallas CN, Banner NR.Quality of life and psychological well-being during and after left ventricular assist device support. Clin Transplant 2007; 21:622-7.
91. McCarthy PM, Savage RM, Fraser CD, Vargo R, James KB, Goormastic M, et al. Hemodynamic and physiologic changes during support with an implantable left ventricular assist device. J Thorac Cardiovasc Surg 1995; 109:409-18.
92. DeRose JJ Jr, Umana JP, Argenziano M, Catanese KA, Gardocki MT, Flannery M, et al. Implantable left ventricular assist devices provide an excellent outpatient bridge to transplantation and recovery. J Am Coll Cardiol 1997; 30:1773-7.
93. Ashton RC Jr, Goldstein DJ, Rose EA, Weinberg AD, Levin HR, Oz MC. Duration of left ventricular assist device support affects transplant survival. J Heart Lung Transplant 1996; 15: 1151-7.