

Ventricular assist devices in current management of advanced heart failure

Rola urządzeń do wspomagania pracy komór serca w leczeniu zaawansowanej niewydolności krążenia

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Heart failure due to systolic dysfunction is characterized by high morbidity and mortality even with maximal medical therapy. Another approach to cardiac replacement is needed because cardiac transplantation remains available only to very select group of patients. Research on the development of mechanical cardiac support has been conducted for more than four decades and has led to development of three types of ventricular assist devices (VAD) which are now available for clinical use: namely, volume-displacement pumps, axial-flow pumps and centrifugal pumps. A competent native aortic valve is essential for the use of all left ventricular assist devices. The decision about the kind of device that will be the best for a given patient is dictated by clinical indicators such as the need for short vs. long term support, emergent vs. elective implantation, indication for left ventricular vs. biventricular support and patient's body size. In general, patients can have three clinical indications for VAD implantation: namely, "bridge to recovery", "bridge to transplant" and "destination therapy".

"Bridge to recovery"

When the recovery of native heart function is anticipated, as it is for some patients with acute myocarditis or postcardiotomy cardiogenic shock, a device is said to be used as a "bridge to recovery". Ventricular assist devices have beneficial effects on myocardial function, which include reversal of the downregulation of beta receptors seen in heart failure and the restoration of the ability of the heart to respond to the inotropic effects of sympathetic stimulation [1].

They also improve geometry of the heart, permitting a process of reverse ventricular remodeling. In patients who require only temporary cardiac support, a percutaneous device or a paracorporeal device, which will not require an extensive explantation procedure, is most appropriate. Recovery of the heart may be monitored by echocardiography and hemodynamic measurements but the decision to explant ventricular assist device is usually quite challenging because there are no widely agreed criteria regarding explantation. There are conflicting data regarding the durability of recovery and the long term outcome of these patients.

Recent data suggest that recovery is also possible in patients with advanced chronic heart failure when medical therapy with intense neurohormonal blockade is used together with ventricular assist devices. In a study of 15 patients with nonischemic cardiomyopathy who were treated with lisinopril, bisoprolol, carvedilol, spironolactone, losartan and a selective beta-2 agonist clenbuterol during the period of LVAD support [2] 11 of 15 patients (73%) had sufficient myocardial recovery to undergo explantation of the assist device. In the group of nine surviving explanted patients, long term follow-up (mean 59 months) showed the mean LVEF remained normal. If further research supports this therapy, we can expect significant expansion of "bridge to recovery" indication for VAD.

"Bridge to transplantation"

In patients, who are candidates for heart transplantation, but who may not survive the waiting period, a ventricular assist device may be used as

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Fig. 1. Volume displacement pump –HeartMate
Ryc. 1. Pompa membranowa – HeartMate

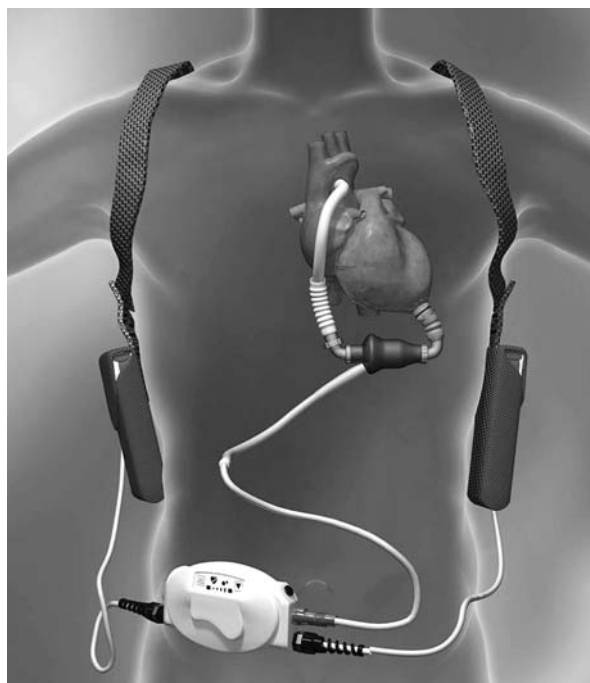


Fig. 2. Diagram showing placement of axial flow pump, driveline, controller and batteries
Ryc. 2. Schemat pokazujący ułożenie przepływowej pompy osiowej, kabla zasilającego, kontrolera i baterii

a “bridge to transplantation”. For this group of patients, pumps that are fully implantable and that offer intermediate or long-term support are optimal. Patients who receive the HeartMate as a bridge to transplantation may have a better short- and long-term outcome compared to patients treated with an intravenous inotrope [3-5]. In the largest reported experience, 243 patients were supported with the HeartMate for a mean of 78 days [5]. Successful bridging to transplantation was achieved in 70% of patients. Post-transplant survival at one, five and ten years was 91, 70, and 40%. Other benefits with the HeartMate include improvement in renal function and reduction in pulmonary hypertension prior to transplantation [3, 4]. A recently published prospective, multicenter study of 133 patients with end-stage heart failure, who were on a waiting list for heart transplantation and underwent implantation of a continuous-axial flow pump VAD showed a 75% survival rate at 6 months and 68% at 12 months, results that compares favorably with previous data. This led to conclusion that a continuous-flow left ventricular assist device can provide effective hemodynamic support for a period of at least 6 months in patients awaiting heart transplantation. This study also demonstrated improved functional status and quality of life while waiting for transplant on axial flow pump VAD [6] (fig. 1 and 2).

The concern regarding VAD support for bridge to transplantation is increased levels of anti-HLA antibody production in patients supported with VAD. It is both because of blood product transfusions at the time of surgery and because the blood-contacting surface of the device is thought to cause lymphocyte stimulation [7]. In a single-center report of 239 patients who received a VAD, the PRA level increased immediately after device implantation, followed by a progressive decrease [8]. Predictors of a higher PRA level in this analysis included time from device implantation, female sex, younger age, higher PRA before device implantation, and greater number of blood transfusions. The type of device used did not have a significant impact on the PRA level.

“Destination therapy”

Finally, for patients who are not candidates for transplantation and for whom recovery of cardiac function is not expected, a mechanical device may be used as “destination therapy”. In this case the device will provide permanent support to the failing native heart. Only the HeartMate XVE (Thoratec Corp, MA), an electrically powered version of the HeartMate device, is currently approved by the Food and Drug Administration for destination therapy. Axial flow devices are currently used in clinical trials to test their application for this indication and their approval for this indication is anticipated.

The role of the HeartMate LVAD as an alternative to optimal medical therapy in patients ineligible for transplant was evaluated in the REMATCH trial, which randomly assigned 129 such patients to the LVAD or optimal medical therapy [9]. In this trial, use of the LVAD was associated with a higher survival at one (52% vs. 25% for medical therapy) and two years (23% vs. 8%), representing a 48% reduction in the risk of death from any cause. Median survival was higher with the LVAD (408 vs. 150 days). These survival rates however, are much lower than those seen with transplantation. Thus, an LVAD should not be considered a substitute for transplantation in patients who are candidates for the procedure. In a later analysis, the survival benefits in REMATCH were seen only in the 91 patients who required intravenous inotropes at study entry [10]. This observation illustrates the importance of limiting LVAD therapy to appropriately selected patients.

A new "bridge to decision" indication is now evolving. With the availability of temporary, percutaneous ventricular assist devices, there may be role for implantation of a temporary device in critically ill patients to optimize their clinical status prior to making decision regarding implantation of expensive permanent device.

Review of available ventricular assist devices

Volume-displacement ventricular assist devices can be used for left ventricular support or for bi-ventricular (right and left) support. The device consists of a pumping chamber connected through inflow cannula with the ventricle, and through an outflow cannula with the artery. They include an inflow and outflow valve (bioprosthetic or mechanical), which allows unidirectional flow through the device. The pumping chamber fills either passively or by suction applied during chamber expansion. The chamber is then compressed by externally applied pressure, causing ejection of blood and generating a pulsatile blood flow. The most widely used volume displacement device is the Thoratec Ventricular Assist Device which has supported patients for up to 3.3 years. It is a paracorporeal system, in which the pump is located outside the body. The paracorporeal devices are positioned close to the abdominal wall and held in place with a hook-and-loop binder, permitting ambulation. Also, with the new portable drive the patients are allowed some mobility. Heparinization is essential to prevent thromboembolic events. The device can be used as a bridge to transplantation or as a bridge to recovery.

The Thoratec Implantable VAD (IVAD) was FDA approved in 2004 for use as a bridge to transplantation and for post-cardiotomy recovery in patients who are unable to be weaned from cardiopulmonary bypass [11]. The implantable Thoratec HeartMate XVE was also

approved as a bridge to transplant, as a bridge to recovery and for destination therapy. The pump in each case is implanted internally and rests below the diaphragm, in the intraperitoneal or properitoneal position with the driveline tunneled under the skin and connected to external power supply. The Thoratec HeartMate XVE device has a unique textured, rather than smooth, surface design for the pumping chamber, which results in the formation of a protein coat, that becomes non-thrombogenic over time. As a result, anticoagulation with warfarin is not required for this device and the thromboembolic rate is below 3%. Implantable devices are designed to permit rehabilitation and hospital discharge. Patients may carry batteries in a specially-designed harness or may use a "carry-on" size power supply on wheels. These devices produce pulsatile flow by mechanical compression of a pumping chamber the pump creates noise in each cardiac cycle. That may be disruptive to the sleep of some patients.

Other volume displacement systems include the implantable Novacor Left Ventricular Assist System (WorldHeart), paracorporeal Abiomed's AB5000 and the total artificial heart. When a total artificial heart is implanted, the patient's own left and right ventricles are removed and the device is inserted orthotopically (in the same anatomical location as the heart). Examples of total artificial hearts include the CardioWest device (SynCardia) and the AbioCor (Abiomed). Total artificial hearts are currently investigational.

The axial-flow ventricular assist pumps contain an impeller: a rotor with helical blades that curve around a central shaft. The spinning of the impeller draws blood from the inflow orifice or cannula through the device to the outflow cannula. There are no mechanical valves. These devices provide continuous rather than pulsatile flow and are totally implantable. Their advantages include small size, low noise, and absence of a compliance chamber. The cable is attached to an external power source, a rechargeable lithium-ion battery that can be worn on the patient's waist. Challenges with axial flow VAD include the need to determine the optimal pump-speed settings to provide sufficient blood flow without ventricular arrhythmias and difficulty in detecting vital signs in a systemic circulation with minimal pulsatility – patients have no pulse and no blood pressure to measure. A previous concern that diminished pulsatile pressure and flow might have unfavorable effects on major organ function has been dispelled [12]. Examples of axial flow pumps include the Jarvik 2000 (Jarvik Heart), the MicroMed DeBakey device (MicroMed), and the HeartMate II (Thoratec). The MicroMed DeBakey and HeartMate II pumps are implanted in the abdomen. The Jarvik 2000 pump is practically encapsulated by the native myocardium. It has no inflow graft, no valves, and

produces a high-flow stream of blood that continuously washes the tiny bearing. Axial-flow impeller pumps are currently investigational. The simplicity of their design translated into a good durability profile, with animal data indicating the possibility of 8 years of uninterrupted function without mechanical failure.

Most ventricular assist devices require cardiac surgery for implantation. Some newer percutaneous devices, however, can be inserted in the cardiac catheterization laboratory. The smallest and least invasive is the Impella pump (Abiomed), an axial-flow pump located on the distal end of a catheter. It is inserted in the femoral artery and advanced retrograde into the left ventricle. Another percutaneous ventricular assist device is the TandemHeart (CardiacAssist), an extracorporeal centrifugal pump whose inflow catheter is placed percutaneously in the left atrium through a transseptal approach and whose outflow cannula is placed in the femoral artery.

Selection of the most appropriate ventricular assist device for a given patient depends on several factors. Patients who require urgent hemodynamic support can most easily be achieved with a percutaneous device. In patients who require only temporary cardiac support, a percutaneous device or a device that will not require an extensive explantation procedure, such as an extracorporeal pump, may be appropriate. Those who require right as well as left ventricular support typically require two pumps. Because it is usually not possible to implant both a right-heart pump and a left-heart pump owing to space constraints, such patients are candidates for extracorporeal pumps. Body size dictates whether the pump can be implanted or needs to be in the extracorporeal position. Volume displacement pumps can not be implanted in children or women with a small body size (body surface area $<1.5 \text{ m}^2$) because their abdominal space will not accommodate this relatively bulky device. Once axial flow pumps are approved they will be preferred choice for smaller size patients because their volume is much smaller.

Despite the wide spectrum of pumps now available, the problems associated with this technology continue to be significant. The issues of infection, bleeding, thromboembolism, and limited mobility have not been resolved. The best data regarding complications associated with volume displacement devices come from REMATCH trial with the HeartMate in which LVAD support was used for destination therapy. Although this therapy was associated with a higher survival at one and two years with VAD [9], in the 68 patients who received the device infection occurred in 28% by three months (mostly in the drive-line tract and pocket) and fatal sepsis occurred in 25% of patients. Complications with bleeding occurred in 42% of patients by six months and the incidence of a peripheral embolic event was 14%

per year, a value not significantly different from complications of medical therapy. The probability of device failure was zero at one year and 35% at two years. A high incidence of bloodstream infections (8 to 9 per 1000 device days) [13], including cases of fungemia and fungal LVAD endocarditis, has also been noted in other reports [13, 14]. The HeartMate may be associated with an increase in de novo episodes sustained monomorphic ventricular tachycardia (VT), most of which occur within the first week and all within two weeks after implantation [15]. Mechanical failure of the HeartMate is most often a consequence of incompetence of the LVAD inflow valve. The Novacor device is known for its durability and low rate of mechanical failure, however, it has a high rate of the incidence of thromboembolic neurologic events approaching 25% even in the presence of adequate anticoagulation with warfarin. In one series, the incidence of thromboembolic events was highest earlier after implantation before the level of anticoagulation was stable; only 10% of patients with a thromboembolism had neurologic sequelae [16]. Bloodstream infection is as common with the Novacor device as with the HeartMate, with 6 cases occurring per 1000 device days in one review [13]. In a series of 25 patients with a median duration of support with the Novacor device of 55 days, 12 (48%) developed LVAD infection [17]. Seven of these patients died with multiple organ failure or other signs of acute infection.

For the axial flow HeartMate II device the most common adverse event was bleeding, primarily in the early postoperative period. Out of 133 patients eight (6%) had an ischemic stroke, and three (2%) had a hemorrhagic stroke. Five of these 11 events occurred within the first 2 days after device implantation. Five additional patients had transient ischemic attacks that were completely reversed. Device-related infection was observed in 14% of patients, with all infections involving the percutaneous lead and none involving the pump pocket. This represent a significantly lower infection rate as compared with volume displacement pumps. The likely explanation for lower infection rate is smaller size of axial flow VAD permitting a more stable position of the device and a less extensive surgical wound [6].

Criteria for selection of patients and predictors of survival

There are several basic criteria for selection of patients for device insertion. The patient should be on maximal inotropic support, with or without IABP, have systolic blood pressure $<80 \text{ mmHg}$ with a cardiac index below $2.0 \text{ l/min per m}^2$ or a pulmonary capillary wedge pressure above 20 mmHg and if implantation is for bridge to transplant patient needs to be a heart transplant candidate. An important consideration in timing the insertion of a device is that the device be

implanted before there is secondary end-organ damage. Implantation will not improve the patient's clinical status if severe HF has led to irreversible end-organ damage. Renal dysfunction especially has been correlated with poor outcomes in several studies. In one report, patients requiring dialysis in the peri-implantation period had a mortality rate of 100% [18]. In another study of 55 patients requiring renal replacement therapy, only 11% survived to transplantation [19].

Analysis of data from 366 patients with an ischemic (27%) or idiopathic (60%) cardiomyopathy who were supported by the Novacor device for a median of 100 days [20] showed the following preimplant conditions predicted mortality: respiratory failure with septicemia, right heart failure, age >65 years, acute postcardiotomy and acute myocardial infarction. The one year survival after implantation of the device for patients without any of these factors was 60% compared to 24% when at least one risk factor was present.

A screening risk score to predict operative mortality after device implantation was developed from an analysis of 130 patients who received a HeartMate LVAD [21]. Operative mortality was 25%. The following risk factors at the time of surgery were found to increase mortality significantly: requirement for ventilator support (4 points), clinical picture of postcardiotomy shock (2 points), use of temporary LVAD prior to HeartMate insertion (2 points), central venous pressure >16 mmHg (1 point), prothrombin time >16 seconds (1 point). The risk score is calculated by adding together the points for all risk factors present in the patient under evaluation. A risk score >5 was associated with a significantly greater operative mortality than a lower score (46 vs. 12%). In another report, patients with a low (0 to 4), intermediate (5 to 7) or high (8 to 10) risk score had increasing mortality rates (8, 32, and 49%) and decreasing rates of successful bridging to transplantation (89, 65, and 49%) [5].

Another predictor of successful LVAD implantation is right ventricular function. Left ventricular assist devices provide support only of left ventricular function but since the left ventricular end-diastolic pressure will drop after the insertion of an LVAD, the afterload of the RV should fall. As a result, even poor RV function before LVAD implantation often improves. Protection of the RV is essential prior to and during LVAD implantation. Elevated right-sided filling pressures should be ameliorated by as much diuresis as can be safely tolerated prior to LVAD insertion to help preserve RV function. If other methods fail, increased pulmonary vascular resistance and right ventricular dysfunction after LVAD implantation can be treated by insertion of an RVAD. However, RVAD insertion in this setting carries a high mortality risk, especially if RVAD support is delayed. In a series of 243 patients who underwent HeartMate implantation, 17 (7%) required RVAD support [22]. Ten RVADs were inserted within 24 hours of surgery; seven of these survived to transplant.

In contrast, of seven RVADs inserted more than 24 hours after surgery, only four survived to transplant.

Timing of transplantation – Ventricular assist device support is increasingly being used as a “bridge” to transplantation and for overt multisystem organ failure when an appropriate donor is not available. Survival for patients transplanted within the first two weeks after VAD implantation and for those transplanted more than six months after device implantation is not as good as for patients transplanted within that interval.

This was illustrated by an analysis of data from the United Network for Organ Sharing (UNOS) on 466 heart transplants performed between 1999 and 2001 after VAD support [23]. Patients transplanted within two weeks of device implantation had a one-year survival of 74%; those transplanted after more than six months had a one-year survival of 76%; and patients transplanted four to six weeks after VAD insertion (the optimal interval) had a one-year survival of 92%. Factors influencing these results include the early deaths of unstable patients, the resolution of end-organ dysfunction after the first few weeks, and the eventual development of device-related complications.

Initial decision making regarding choice of VAD and implantation of VAD, management of postoperative complications and rehabilitation of patient with VAD only opens the door to the complexity of outpatient management of patient with VAD. Only well organized programs with 24/7 on-call support and dedicated team are able to provide fast response system to many issues associated with chronic VAD support. The reward is enormous and translates to good quality of life of supported patients and their families (fig. 3).



Fig. 3. VAD patients of Indiana University/Clarian Advanced Heart Care Program during their third “Second Chance Heart Club” reunion

Ryc. 3. Grupa pacjentów Indiana University/Clarian Advanced Heart Care Program w czasie trzeciego dorocznego spotkania „Klubu Serca Drugiej Szansy”

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