

The ventricular assist device: a bridge to ventricular recovery, a bridge to heart transplantation or destination therapy?

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Abstract

Despite advances in pharmacological treatments aimed at a neurohormonal blockade for heart failure, there is still a growing number of patients with advanced symptoms who suffer significant morbidity and mortality. At present the most effective cure for end-stage congestive heart failure is cardiac transplantation. This method is severely limited owing to a lack of available organs. This is why ventricular assist devices (VADs) capable of completely supporting the circulation are taking on an increasingly important role in heart failure therapy. VADs are important bridges to cardiac transplantation. The Randomised Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) trial revealed that they could be used as long-term destination therapy for non-transplant candidates. The latest studies show that VAD support may also function as a bridge to ventricular recovery and enable this procedure to take place. Apart from foreign devices, there is the Polish system (PCAS), which is being prepared for introduction into global practice. (Cardiol J 2007; 14: 14–23)

Key words: heart failure, ventricular assist device, cardiac transplant

Introduction

Heart failure is now acknowledged to be the most common malignant disease in industrialised countries, with advanced heart failure having a worse prognosis than most forms of cancer [1]. Advances in pharmacological treatment have helped patients in all stages of systolic dysfunction, even those with NYHA IV symptoms [2–4]. The Working Group on Heart Failure of the European Society of Cardiology has promoted a number of initiatives aimed at improving the treatment of heart fail-

ure [5]. However, even the best combination of ACE inhibition, β -blockade and diuretics is only able to confer a survival benefit up to 16% at one year, and this benefit disappears by year five [6]. Mechanical stresses on the myocardium (increased preload and afterload) and chronic neurohormonal activation conspire to propagate the maladaptive ventricular remodelling responsible for the insidious nature of heart failure. Recent studies suggest that further pharmacological neurohormonal blockade may be neither safe nor effective [7]. This finding has led to the concept that the limit to which neurohormonal and cytokine mechanisms can be blocked in heart failure patients has already been reached [8]. The problem of how to treat patients worldwide who develop advanced heart failure despite optimal medical therapy has not yet been resolved [9].

Transplantation provides the most effective therapy for this condition, but the shortage of donor organs has resulted in the US of fewer than 10% of

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potential recipients actually receiving a transplant [10]. This situation has forced scientists to search for alternative methods of treatment. At present end-stage chronic heart failure is a significant clinical problem as well as a subject of scientific interest.

Transplant candidates whose disease reaches its final stage before an appropriate donor heart becomes available might be considered eligible for temporary or permanent mechanical circulatory support (MCS). The concept of circulatory assistance is not new. The need for such temporary support for hours or days has been recognised for over 60 years and still exists [11]. It is recognised that device-based approaches, ranging from the use of devices for monitoring patient status in order to anticipate exacerbation of congestive heart failure and pre-emptively adjust therapy to the application of devices for supporting preterminal patients with end-stage disease, will assume an increasingly important role in treating the growing number of patients with advanced heart failure [12].

MCS was first used clinically in 1953 with the implementation of cardiopulmonary bypass [13]. This breakthrough led to numerous surgical treatments for a variety of cardiac disorders. The success of cardiopulmonary bypass stimulated research into other innovative techniques for supporting the circulation. Counterpulsation with the intra-aortic balloon pump was first applied clinically in 1967 to support patients with acute heart failure [14].

Since 1953 congestive heart failure patients were occasionally supported temporarily by cardiopulmonary bypass [15], an implantable ventricular assist device (VAD) [16] or a totally artificial heart (TAH) [17]. Although the overall success rate was limited, this early experience did prove that MCS could adequately sustain a patient's circulation until cardiac function recovered or a donor heart could be obtained. In the early 1980s the introduction of cyclosporine-based immunosuppression allowed heart transplantation to become a widely accepted therapeutic alternative. During the same decade clinical trials were initiated to evaluate the safety and efficacy of MCS systems in supporting terminally ill transplant candidates until a suitable donor heart could be found. The use of a wearable ventricular assist device (VAD) in the treatment of advanced heart failure has steadily increased since 1993, when these devices became generally available in Europe.

Devices for the treatment of heart failure

Numerous devices are now approved by the Food and Drug Administration (FDA) for therapy

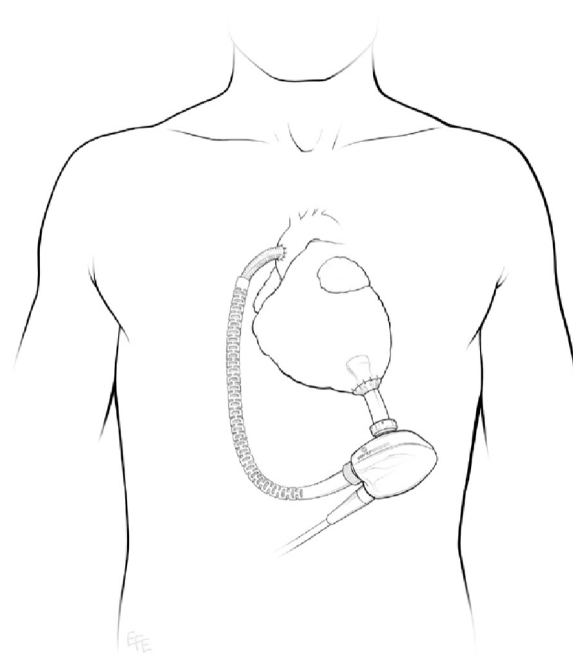


Figure 1. The diagram of the left ventricular assist device.

in acute heart failure and in chronic decompensated congestive heart failure. We would like to focus attention on the ventricular assist device used as a bridge to transplant and, most recently, as destination therapy in patients ineligible for transplantation [18]. These devices can be divided according to site of placement (commonly extra-, para- or intra-corporeal) and type of flow generator system (centrifugal, axial or diaphragm). A left ventricular assist device is shown diagrammatically in Figure 1.

VADs — indications for support

Because of the limited availability of donor organs and the urgency of cardiac support in settings of severe haemodynamic decompensation ventricular assist devices capable of completely supporting the circulation are taking on an increasingly important role in heart failure therapy.

MCS is life saving in patients who fail to improve or stabilise with intravenous inotropes or vasodilators, intra-aortic balloon-pump support and mechanical ventilation [19].

Haemodynamic criteria for VAD insertion are as follows:

- cardiac index $< 2 \text{ L/min/m}^2$;
- systolic blood pressure $< 90 \text{ mm Hg}$;
- pulmonary capillary wedge $> 20 \text{ mm Hg}$;
- urine output $< 20 \text{ ml/h}$.

When these are found despite pharmacological support, optimal fluid loading and use of IABP as

appropriate. Each case is assessed individually and these criteria are used as a guide only. Some patients have the VAD inserted prior to these criteria being met [20].

In planning the application of the assist device we must decide whether one or both ventricles require support. Insertion of an implantable VAD complicated by early right ventricular failure has a poor prognosis and is largely unpredictable. Patients with risk factors for right ventricle dysfunction (the need for circulatory support, female gender, non-ischaemic aetiology) may best be treated with a biventricular assist device or a TAH [21].

The next questions arising are whether the VAD should be implanted as a bridge to transplantation or as destination therapy and how long mechanical support will be required.

Selection of the appropriate device depends on a number of considerations, including the anticipated duration of patient support, the need for right-side support and the patient's size. Excluding of the strict contraindications to VAD, insertion is very important.

The following are contraindications to VAD insertion:

- irreversible hepatic/renal failure;
- active systemic infection;
- chronic obstructive airway disease;
- carcinoma with metastases;
- significant blood dyscrasias;
- cerebral vascular disease.

Ventricular assist devices

There are currently five FDA-approved VADs in addition to the intra-aortic balloon pump. Extracorporeal devices include the ABIOMED BVS 5000 and Thoratec, which are both capable of biventricular assistance. Novacor N1000PC (World Heart Corp), HeartMate Pneumatic (Thoratec Corp), and the Vented Electric LVADs are implantable devices designed for left ventricular support.

The next generation of devices consists of axial flow pumps with a non-pulsatile flow, totally implantable LVADs (Arrow LionHeart, WorldHeart Heart Saver) with transcutaneous energy transfer and the Total Artificial Heart (CardioWest, AbioCor).

At present devices are being used for univentricular or biventricular support (Fig. 2). For left support the inflow cannula is placed in either the left atrial appendage, the left atrium via the interatrial groove or the left ventricular apex. The outflow cannula returns blood to the ascending aorta. For right heart support atrial cannulation is used with the outflow cannula returning blood to the pulmonary artery.

Extracorporeal devices

The ABIOMED BVS 5000 consists of two extracorporeal pneumatic pulsative pumps that can be used for univentricular or biventricular support. The advantages of this support system are its ease of use

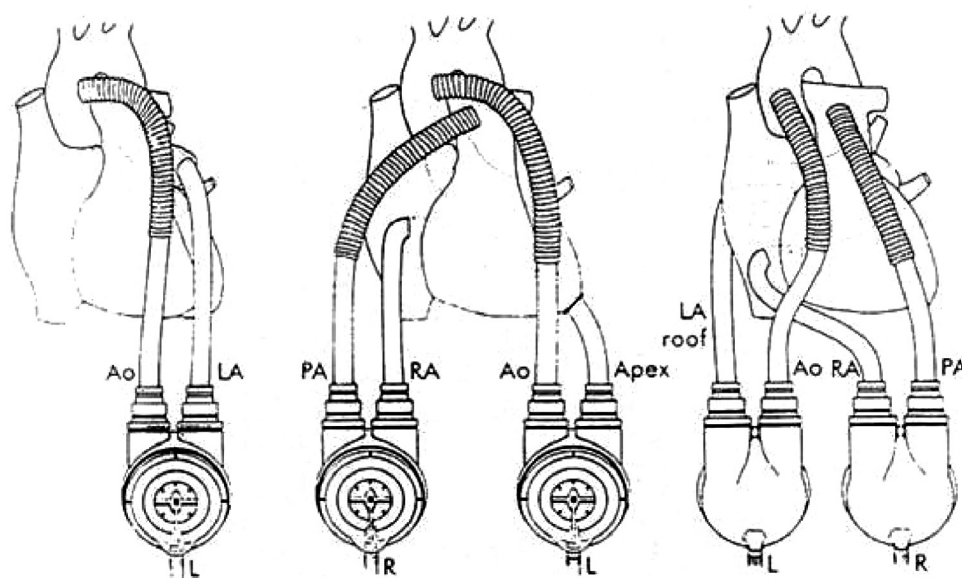


Figure 2. Diagram shows the Thoratec device used as a univentricular or biventricular assist device (From Farrar DJ, Hill JD, Gray LA et al. *N Engl J Med*, 1988; 318: 333).

and availability. It is typically used for periods up to seven days.

The thoratec paracorporeal pump is a pneumatically driven polyurethane sac designed for long-term use. The Thoratec VAD system is indicated as a bridge to transplantation and a bridge to recovery. The main advantages of this device include its versatility for biventricular support and its suitability for use in small patients. Patients require anticoagulation for the duration of the Thoratec VAD implantation.

Intracorporeal devices

The HeartMate LVAD is typically implanted in a preperitoneal pocket (it can also be in an abdominal location) anterior to the posterior rectus sheath and just below the left costal margin. There are two types of HeartMate device:

- the Implantable Pneumatic LVAD (IP-LVAD, Thoratec Corp) is powered and controlled by an external pneumatic drive console that rests on a wheeled cart;
- the Vented Electric LVAD (VE-LVAD) contains an electrical motor within the blood-pump housing. It receives external power and control signals from an external microprocessor via a vented driveline.

Both systems have porcine valves and textured blood-contacting surfaces that become covered by a “pseudointimal” layer. This results in a very low incidence of thromboembolic events, and therefore patients do not require systemic anticoagulation. An increasing number of patients are being discharged from hospital after implantation of the VE-HeartMate. Insertion of the HeartMate is difficult in patients with a body surface area (BSA) less than 1.5 m² because of anatomical constraints.

The Novacor is an implantable electrical dual pusher plate device designed for long-term cardiac support. Like the HeartMate, it can be used only for left-side support and in patients with a weight of over 60 kg. The device has a percutaneous lead that serves as both a vent and an electrical connection. The Novacor LVAD device requires systemic anticoagulation to prevent thromboembolism. Even with this, however, the risk of thromboembolic complications with the Novacor LVAD remains high [22]. The advantages of this system are the excellent mechanical reliability and successful outpatient experience.

The Arrow Lionheart-2000 is an experimental LVAD. The battery, controller and a gas compliance chamber are implanted with no lines crossing the

skin. The pump is powered by means of continuous transcutaneous energy transfer that maintains the charge on the battery. The battery can operate the device for approximately one hour when not being charged, but only 20–30 min daily is recommended. The device was designed for destination therapy [12].

Device selection

Device selection depends not only on specific patient characteristics and the pathology of the patient’s heart failure but also on device characteristics, device availability and the experience of the surgical team [23, 24]. Patients in profound cardiogenic shock require support to avoid permanent end-organ dysfunction and increase their chances of survival. The preferred devices are the ABIO-MED BVS 5000 or Thoratec device. These devices may provide full biventricular support, re-establishing near normal haemodynamics while myocardial recovery is awaited. If prolonged support is expected, conversion to a longer-term device such as an implantable LVAD or TAH should be considered. The Thoratec device has the advantage of providing long-term, extracorporeal support.

Device selection for long-term support is much more complicated and is often subjective and based on the surgeon’s experience. For smaller patients (BSA < 1.5 m²) the Thoratec device and perhaps a continuous flow pump are the only options. For the larger patient all devices are potential options. An implantable LVAD is used most frequently, but the CardioWest (now renamed “Syncor”) is useful for severe biventricular failure. The role of the continuous flow pump remains to be defined. Currently there is no approved device to provide permanent MCS, although an FDA advisory panel has recommended conditional approval for the HeartMate VE LVAD [22].

New devices

Axial flow devices

The newest generation of devices includes axial flow and centrifugal pumps. The most modern axial flow devices offer significant potential advantages over earlier devices, because they are smaller, simpler and less obtrusive to the patient, yielding a better quality of life. The blood flow is essentially non-pulsative and pump output is dependent mainly on afterload. In addition, because of their smaller size, they can be used in smaller patients, including children [25]. Two axial flow

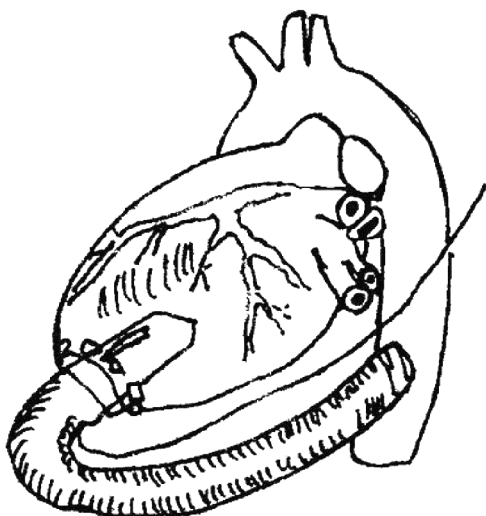


Figure 3. The Jarvik 2000 pump in the ventricular apex.

pumps are in current use: the MicroMed/DeBakey VAD (MM-D VAD) and the Jarvik 2000 Heart, which have certain similarities in design and function.

The Jarvik 2000 Heart, in particular, has many advantages. Its implantation can be performed without median sternotomy, which makes the eventual transplantation operation easier. There is no inflow cannula, which rids the patient of the thrombotic and haemolytic problems encountered with inflow cannulae. Circulation to the coronaries, the brachiocephalic, the left carotid and the subclavian arteries is thus provided by retrograde flow. There is no need for an external pocket in the mediastinum or the peri-peritoneum, which decreases the risk of infection [26]. Figure 3 shows the Jarvik 2000 pump in the ventricular apex.

The MicroMed/DeBakey VAD consists of a titanium inflow cannula that is inserted into the left ventricular apex and leads to the pump proper, which connects to the ascending aorta via a vascular graft. The pump is implanted through a median sternotomy in a small extracardiac pocket [27].

The HeartMate II LVAD is an axial flow pump that has a spinning rotor as its only moving part. The HeartMate II has a left ventricular apical inflow cannula with a sintered titanium blood-containing surface. No compliance chamber or valves are necessary. The outflow cannula is connected to a Dacron graft, which is then anastomosed to the ascending aorta in a similar fashion to that achieved with the original HeartMate XVE. The pump is designed to deliver as much as 10 L/min of cardiac output and is placed either intraperitoneally or

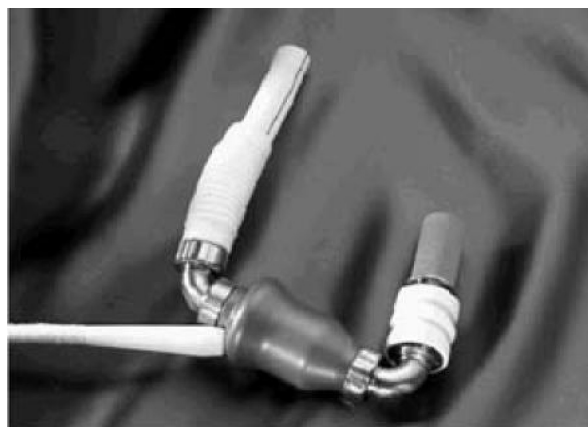


Figure 4. HeartMate II left ventricular assist device.

extraperitoneally [28, 29]. The HeartMate II LVAD is shown in Figure 4.

Centrifugal pumps

Centrifugal pumps utilise the pump mechanism of a standard heart bypass. Two of the most common are the Medtronic-Biomedicus pump and intracorporeal devices, while the latest extracorporeal centrifugal pumps are becoming increasingly popular. New centrifugal systems include the bearingless system. This drive system is magnetically coupled to an external power source and pump flow is related to rotation speed. The advantages of the centrifugal pump are simplicity of design, versatility and the relatively low costs of manufacture and operation. It can be used as a femoral-femoral bypass or as a left (right) ventricular-to-aortic (pulmonic artery) bypass. Its main disadvantages are the need for heparinisation, difficulty in chest closure, the need for intensive monitoring and the inability to generate a pulsatile flow. The pump is used primarily as a bridge to recovery in cardiogenic shock. The total duration of support with a centrifugal pump is usually limited to no more than two to three weeks [30].

Intracorporeal centrifugal devices

The Ventrassist implantable rotary blood pump is a hydrodynamically suspended electromagnetically driven centrifugal blood pump that provides a continuous flow of up to 10 L/min at a low rotational speed and power consumption level [31].

The HeartQuest ventricular assist device is an advanced device with full magnetic suspension of the rotor designed to address specific clinical shortcomings in existing devices and to maximise

margins of safety and performance for an implantable assist device. The dimensions of this device are 35×75 mm and it has a total weight of 440 g. Animal study results have been very promising with clean surfaces seen in a 116-day experiment and no anticoagulation after day 43 [32].

The extracorporeal centrifugal pump

The Levitronix Centrimag short-term ventricular assist device is a centrifugal pump designed for extracorporeal short-term support that operates without mechanical bearings and seals. The rotor is magnetically levitated so that rotation is achieved without friction or wear, which seems to minimise blood trauma and mechanical failure [33].

Percutaneous assist devices

Some of the new percutaneous assist devices (pVADs) are currently being explored in clinical trials. The TandemHeart pVAD is a continuous-flow centrifugal pump designed to provide up to 4.0 L/min of systemic blood flow. The pump requires a priming volume of 10 mL. The device can be rapidly inserted in the catheterisation laboratory using a standard trans-septal approach. The inflow cannula is inserted into the femoral vein and is advanced across the interatrial septum into the left atrium. The outflow cannula returns oxygenated blood to the femoral artery. The Cancion system consists of a centrifugal pump connected to the circulation via a graft cannula anastomosed to the left axillary artery and a percutaneous cannula placed into the left common femoral artery. Flow is initiated from the femoral to the axillary artery. The Impella Recover 100 is a new intravascular microaxial blood pump for use as short-term mechanical support for cases of acutely reduced left ventricular function. These systems have quickly and effectively improved the patient's haemodynamics, suggesting that they may one day become a short-term alternative to high-dose inotrope therapy and that their application may delay the need for more invasive forms of mechanical circulatory support [34–36].

Total artificial hearts

Ventricular assist devices support the failing heart by bypassing one or both ventricles. In certain cases, such as myocardial tumours, graft failure, transplant rejection, endocarditis and intracardiac thrombus formation, it may be advantageous to excise the heart and replace it with an artificial device. Total artificial hearts are intracorporeal devices designed for this



Figure 5. Diagram of the AbioCor Artificial Heart.

purpose. Two of these kinds of device are currently in use.

The AbioCor Artificial Heart (new name) is completely implantable in the orthotopic position and has an internal battery and a transcutaneous energy transfer system that enables the battery to be recharged or the device to be run with an external coil (Fig. 5).

The CardioWest Total Artificial Heart was recently approved for use under an FDA investigational device exemption. This device is pneumatically driven and is implanted in the orthotopic position. Dual pneumatic drivelines exit transcutaneously to a console control system that monitors pump pressures and performance. Antiplatelet and systemic anticoagulation are needed. This device is used as a bridge to transplantation in patients with biventricular failure [37].

Total artificial heart pumps are too large to be completely implanted in children or other patients with body surfaces smaller than 1.7 m^2 . In these smaller patients extracorporeal devices must be used for biventricular assistance.

Ventricular assist devices in clinical studies

The use of left ventricular assist devices (LVADs) as an alternative to heart transplantation

(destination therapy) is on the clinical threshold. The Randomised Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) trial compared medical treatment with the electrically driven HeartMate device (Thoratec Corp) in functional class IV patients who were not heart transplantation candidates. Survival in the LVAD group was equal to or better than that in those with medical management at all time points after randomisation for patients undergoing baseline inotropic therapy. By six months survival in this population was 60% with LVAD compared to 39% without. At one year survival was doubled by LVAD: 49% compared to 24% without. By two years survival with LVADs was 28% compared with 11% for current medical therapy [38]. In addition, Mancini et al. [39] have recently demonstrated that LVAD patients can achieve a near-normal exercise response, equivalent to that of patients with mild heart failure, and Dew et al. [40] have shown that patients with a LVAD enjoy a quality of life that is comparable to that of transplant recipients.

Experience with MCS has been gained mainly with patients who are being supported temporarily and for whom it is a bridge to transplantation. One important observation during this experience has been that some hearts recovered sufficient function to have the device removed. For example, the majority of Novacor applications have been employed as a bridge to transplantation, but a growing number of patients are now implanted with a view to recovery of native left ventricular function. A recent single-centre publication has demonstrated that as many as 24% of supported patients may recover sufficient ventricular function to allow them to be weaned from the LVAD [41].

In a study conducted in Pittsburgh VAD as a bridge to recovery was seen in 6.5% of cases overall and in 11% of non-ischaemic patients and was most successful with acute inflammatory cardiomyopathy or post-partum cardiomyopathy [42]. The bridge to recovery is most successful in patients with postsurgical cardiac failure, acute myocarditis and AMI.

However, Dandel's et al. study [43] showed that restoration of heart size and function can be obtained by LVAD support even in patients with advanced idiopathic dilated cardiomyopathy, a disease that, until recently, was considered to be almost irreversible. This research revealed that for selected patients with idiopathic dilated cardiomyopathy weaning from LVADs is a clinical option with good results over nine years and should be considered in those with cardiac recovery after LVAD implantation.

The potential reversibility of myocyte contractile defects is suggested by studies in which isolated failing myocytes obtained from hearts that had been supported with a LVAD manifested improved shortening and relaxation compared with myocytes isolated from hearts that had not been supported with a LVAD [44]. Although this interesting study did not directly address the mechanism for this finding, two recent studies may provide a partial explanation. In the first study support with a LVAD was shown to improve the force-frequency relationship of isolated strips of ventricular tissue and bring about improvements in gene encoding for proteins involved in Ca^{2+} handling (sarcolemmal calcium ATPase, the ryanodine receptor, and the sarcolemmal sodium-calcium exchanger) [45]. In the second study LVAD support led to a restoration of the integrity of the dystrophin cytoskeleton, which had been shown to be disrupted in myocytes from failing hearts [46].

Given the shortage of donor organs, all patients undergoing MCS should be systematically evaluated for evidence of myocardial recovery [47, 48]. Future medical therapies are now being tested.

Researchers at the University of Pittsburgh Medical Center injected stem cells obtained from each patient's own bone marrow into between five and ten heart-failure patients from the time of implantation with a LVAD to heart transplantation. According to the lead investigator, Dr. Amit Patel, the purpose of the new trial is to place the stem cells into the areas of damaged cardiac tissue and then, when the heart is removed to be replaced with a donor organ, to see what has taken place.

In Patel's new study in the USA a portion of heart muscle will be injected with 25 million to 45 million stem cells that have been isolated from the patient's own bone marrow. Ordinary blood serum will be injected into another portion of the tissue for purposes of comparison. The procedures will be performed when the patient receives the assist device to bolster heart pumping. As well as taking various measurements, the researchers will reduce the output of the heart pump about three months after implantation to see if the heart is recovering. The diseased heart will be removed when a donor organ is available for transplant, perhaps six to nine months later, so that the impact of the injected cells may be seen. Researchers suspect that the stem cells, which have the ability to generate specialised cells, could produce cardiac cells and new blood vessels in impaired tissue, and it is likely that some cells will fuse with weakened heart cells [49].

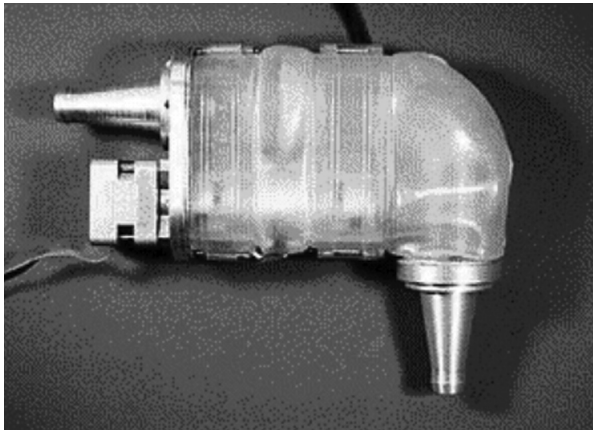


Figure 6. Completely implantable electrohydraulic POLHIVAD.

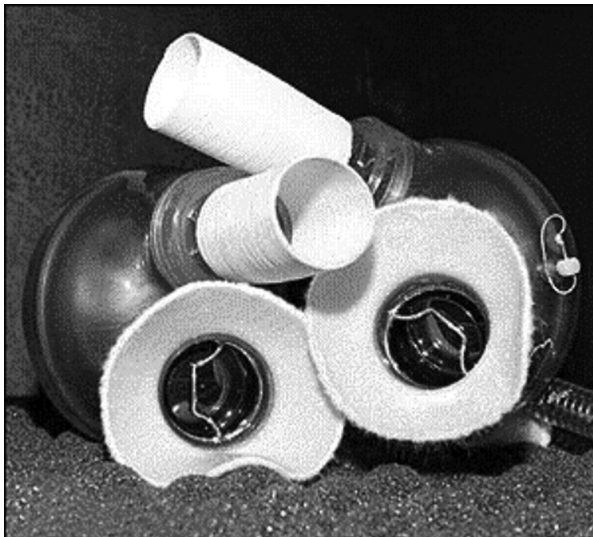


Figure 7. The Polish artificial heart POLTAH.

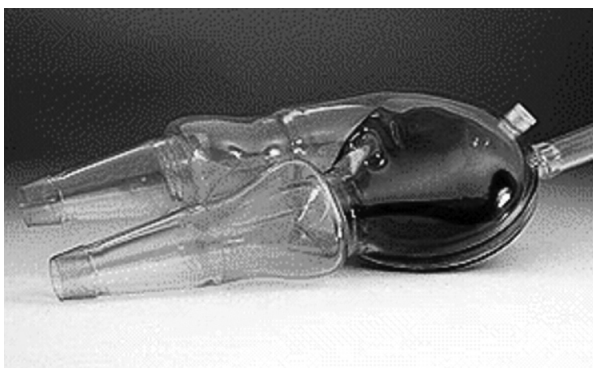


Figure 8. Supporting ventricle POLVAD-PUV with polyurethane valves.

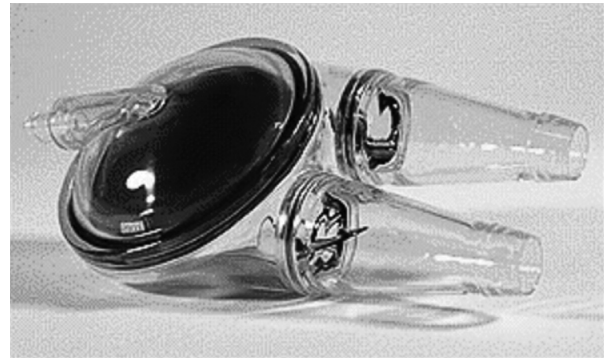


Figure 9. POLVAD-MEV ventricle with mechanical valves.

An alternative mode of treatment involves the use of clenbuterol (a β_2 agonist) for the improvement of cardiac function and exercise capacity in LVAD patients. The process of reverse remodeling of the unloaded left ventricle must be studied in prospective multicentre trials.

The artificial heart could, according to the Cardiosurgical Development Foundation in Zabrze, save the life of several thousand patients a year. Foreign devices are extremely expensive and Polish ones may be as good but much cheaper. The Polish cardiac assist system (PCAS) consists of an extracorporeal ventricular assist device (POLVAD II), a complete heart prosthesis (POLTAH II) and heart-supporting ventricles (PCAS DU 401). At present the system is being prepared for introduction into global practice (Figs. 6–9).

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