

Case Report

First Human Implantation of a New Rotary Blood Pump: Design of the Clinical Feasibility Study

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Surgical treatment of heart failure is emerging as one of the most challenging clinical dilemmas for patients with end-stage cardiac failure not amenable to medical treatment. One of the most intriguing techniques is the use of implantable left ventricular assist devices (LVADs) as a bridge to recovery.

The early experience from our centre has shown that even short term post-cardiotomy mechanical assistance, after heart failure surgery, improves patient outcome; thus, a clinical feasibility study was designed. The hypothesis of the study is that reparative heart failure surgery combined with postoperative mechanical support, ventricular resynchronisation where indicated, and pharmacological treatment can maximise myocardial recovery. In the study a new, implantable, magnetically levitated, rotary pump will be used as a bridge to recovery.

In this manuscript the first worldwide human implantation of a new, continuous-flow LVAD, the WorldHeart Rotary Pump (Levacor™, WorldHeart Inc., Oakland CA), is reported. The design and the rationale of the feasibility study, the inclusion and exclusion criteria, and the primary and secondary end points of the clinical investigation, are delineated. In addition, the design of the new rotary pump, its general principles of operation, and the implantation technique are described.

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The progression of ventricular dysfunction is accompanied by changes in all the different components of the heart, leading to alterations in ventricular geometry and function that can be defined as cardiac remodelling.¹ Cardiac remodelling is a bidirectional process that acts through complex pathways.¹ Despite advances in the pharmacological therapy for heart failure in the setting of left ventricular dysfunction, there is still a growing number of patients with advanced symptoms who suffer significant morbidity and mortality. Recent studies suggest that left ventricular assist devices (LVADs) could promote “reverse remodel-

ling, and improve prognosis” by reversing the ventricular and systemic abnormalities which characterise end-stage heart failure.² It is recognised that device-based approaches will assume an increasingly important role in treating the growing number of patients with advanced heart failure.²

LVADs have been used for long-term support in patients with rapidly deteriorating end-stage heart failure as a bridge to transplantation or more recently as “destination” therapy in patients who are not candidates for transplantation.^{1,3} During the extended use of these devices myocardial recovery at structural, cellular, molec-

ular, and functional levels has been observed,^{1,2,4-16} and improved or near normal cardiac function was noted after device explantation, for varying periods of time, sometimes over several years.¹ Thus the concept of “bridge to recovery” was born.¹

There is accumulating evidence that unloading the left ventricle (LV) with LVADs in end-stage heart failure patients promotes reverse remodelling and left ventricular recovery that can allow device explantation in a selected subgroup of patients.^{1,10,11,17-28}

However, there are no well established prognostic indices of cardiac recovery.^{17,20,25,28} Moreover, neither patient selection criteria²⁷ nor the duration of mechanical support required for lasting recovery have been clearly defined.^{10,11,17,27,29}

In an attempt to maximise myocardial recovery and to address concerns about the percentage of patients who might benefit from the procedure²⁴ and the durability of the recovery, a new strategy has been developed. The Harefield protocol includes a combination of mechanical support with pharmacological treatment to induce maximal reverse remodelling, followed by physiologic cardiac hypertrophy using a selective β_2 -adrenergic receptor agonist.¹

The rationale of our strategy is that reparative heart failure surgery combined with postoperative mechanical support, ventricular resynchronisation where indicated, and pharmacological treatment can maximise myocardial recovery and decrease the duration of the assistance required.

Methods

Design of the clinical investigation

This is a single centre, non-blinded, non-randomised, prospective clinical feasibility study. The objectives of this study are: a) to observe the performance of the WorldHeart Rotary Pump LVAD (Levacor™), as a short term left ventricular support device used as “bridge to recovery”; and b) to gather data to demonstrate that the device is safe and effective when used for temporary mechanical circulatory support.

All experimental procedures were carried out in accordance with the ethical standards of the responsible institutional committee for human experimentation and with the Helsinki Declaration of 1975, as revised in 2000.

The intended use of the device is to provide temporary mechanical circulatory support to the body, while permitting the heart to rest and recover in the

postoperative period of heart failure surgery (repair of functionally regurgitant mitral valve, and when required coronary revascularisation, concomitant left ventriculoplasty, repair of functionally regurgitant tricuspid valve). Suitable candidates are patients suffering from end-stage heart failure due to ischemic or idiopathic dilated cardiomyopathy, whose cardiac condition continues to decompensate despite optimal medical treatment, who are at risk of death, are being referred for heart failure surgery, and who satisfy the study’s inclusion and exclusion criteria, as shown in tables 1 and 2.

Duration of circulatory support

The intended period of circulatory support with the WorldHeart Rotary Pump LVAD as a bridge to recovery is 30-90 days. If recovery is not achieved within this period, and is not anticipated in the near future, the device can be used as a bridge to a well proven LVAD (Novacor), which can be used as destination treatment.

Endpoints of the clinical investigation

The primary endpoints of the clinical investigation are survival to explant, survival to discharge, and all-cause mortality at discharge. The safety endpoints – while the device is implanted – are mechanical failure of the device, incidence of adverse events such as infection, haemolysis, thromboembolic events, neurological dysfunction, bleeding, arrhythmia, renal failure, hepatic dysfunction and any reason for early removal of the device due to patient adverse event or safety.

Table 1. Inclusion criteria.

1. Patients or their legal representatives have signed an informed consent.
2. Patients must be >18 years of age.
3. Patients must have a body surface area >1.2 m².
4. Patients must exhibit New York Heart Association class III or IV heart failure symptoms.
5. Patients must have ejection fraction <28%.
6. Patients must have diagnosis of severe functional mitral regurgitation due to ischaemic or idiopathic dilated cardiomyopathy.
7. Patients must meet the following haemodynamic criteria,
 - a. Pulmonary capillary wedge pressure >18 mmHg, and
 - b. Cardiac index <2.2 L/min/m² or systolic blood pressure <90 mmHg.
8. Female patients of childbearing potential must have negative pregnancy test.

Table 2. Exclusion criteria.

1. Aetiology of heart failure due to or associated with uncorrected thyroid disease, obstructive cardiomyopathy, or pericardial disease.
2. Presence of any mechanical cardiac valve prosthesis.
3. Aortic regurgitation >2+.
4. Ventricular tachycardia unresponsive to all conventional medical treatment.
5. Known history of liver cirrhosis or portal hypertension.
6. Severe hepatic dysfunction defined as ALT/AST and T-bilirubin >3 times upper normal limit.
7. Fixed pulmonary hypertension with PVR >480 dynes.s.cm⁻⁵, unresponsive to pharmacologic intervention, O₂, NO etc.
8. Patients with severe chronic obstructive pulmonary disease as evidenced by FEV1 <1.5 l/min or restrictive lung disease.
9. Prolonged intubation.
10. Any contraindications to surgery or anticoagulation.
11. Severe blood dyscrasia as evidenced by INR >2.5, PT >16.0, PTT >45.0, and platelet count <50,000 U, unresponsive to therapy.
12. Stroke, TIA or history of either within the last 6 months.
13. Significant peripheral vascular disease accompanied by rest pain or extremity ulceration.
14. History of psychiatric disease or irreversible cognitive dysfunction.
15. Creatinine >3 mg/dl.
16. Active systemic infection.
17. Cancer - unresolved malignancy.
18. Severe illness, other than heart disease, which would limit survival to less than 1 year.
19. Recent pulmonary embolus (<2 weeks).
20. Severe cardiac cachexia.

ALT/AST – alanine aminotransferase / aspartate aminotransferase; FEV1 – forced expiratory volume in 1 second; INR – international normalised ratio; PT – prothrombin time; PTT – partial thromboplastin time; PVR – pulmonary vascular resistance; TIA – transient ischaemic attack.

Description of the World Heart Rotary Pump (LVAD)

The major components of the LVAD are a bearingless, centrifugal blood pump, and a microprocessor-based controller. The implanted portion of the device includes an integrated pump/motor unit, inflow cannula and outflow extension, and percutaneous cable carrying the control and power leads. This single compact unit is implanted anteriorly within the left upper quadrant of the abdomen. The pump inflow cannula pierces the pericardial portion of the diaphragm to receive blood from a rigid tip inserted, via the apex, into the left ventricular cavity. The outflow extension is anastomosed to the ascending aorta. (Figures 1, 2). The controller is located extracorporeally, connected to the implanted pump motor via a percutaneous lead.

The pump has a circular chamber with tangential inflow and outflow conduits and is symmetrical about its midplane. The pump drive unit consists of a smooth-surfaced titanium housing (Figure 3) and a magnetically levitated, smooth-surfaced titanium impeller which serves as the rotor. The pump uses opposing permanent magnets and electromagnets, which act to lift or 'levitate' the rotor, resulting in complete suspension, with no physical contact with the pump housing during normal operation. This magnetic levitation

design provides a reliable magnetic suspension allowed by the laws of physics and affords greater flow control than conventional centrifugal pump technology. Having only one moving part, eliminating all mechanical bearings, creating no wear or frictional heat, it is expected to have increased longevity.

The portable control system (containing the pump controller), located extracorporeally, provides properly conditioned power to the implanted pump unit, controlling the pump operation based on pre-programmed control algorithms and adjustable control parameters. In addition, the pump controller monitors LVAD operation and activates alarms for out-of-limit conditions, displays waveforms and numeric data, and provides battery support for patient transport or ambulation.

General principles of operation

The LVAD pump is inserted, in terms of blood flow, between the apex of the left ventricle and the aorta, in parallel with the aortic valve. The LVAD thus presents an alternative outlet for ejection from the LV (versus ejection through the aortic valve).

The relatively low filling resistance of the LVAD inflow tract, combined with the high compliance of the LVAD pump, permits the LV to eject

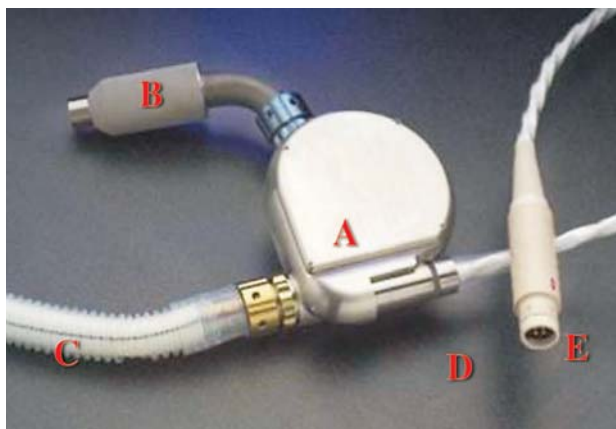


Figure 1. Anterior aspect of the pump drive unit, the assembled inflow and outflow conduits, and the percutaneous lead.

- A. Anterior aspect of the smooth titanium housing of the pump drive unit.
- B. The rigid inflow conduit is assembled at the inflow port of the pump drive unit
- C. The outflow conduit is assembled at the outflow port of the pump drive unit.
- D. The proximal end of the percutaneous lead is fixed to the pump drive unit.
- E. The free end (shown) plugs into the Compact Controller's pump receptacle (not shown).

into the pump at a pressure substantially below systemic pressures; the pump then discharges its contents into the aorta, performing the work of circulation. The workload of the LV is thereby effectively reduced.

The LVAD functions on a continuous flow basis, which is controlled by the differential pressure between the outflow and inflow and the pump speed (the frequency at which the rotor spins in revolutions per minute). The LVAD operates under conditions of any prevailing heart rate, from cardiac arrest (0 bpm) to extreme tachycardia (>180 bpm).

Biocompatibility

All blood-contacting materials and all tissue-contacting materials are tissue compatible. Flow characteristics are acceptable over the specified range of operation. The system is designed not to create clinically significant levels of haemolysis. No electrical connection exists between the internal electrical wiring of the pump drive unit and the patient.

LVAD recipients should be maintained on anti-coagulant therapy and should not be exposed to magnetic resonance imaging.

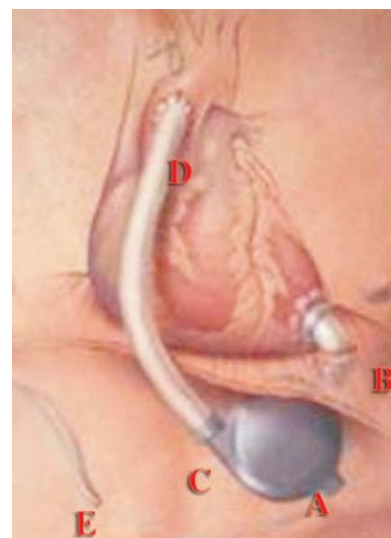


Figure 2. Implanted components of the left ventricular assist device. The implant consists of the pump, the inflow and outflow conduits, and the percutaneous lead.

- A. The pump is implanted below the diaphragm within the left upper quadrant of the abdomen.
- B. The rigid inflow blood conduit is connected to the left ventricular apex and the inflow port of the pump drive unit, and carries blood from the left ventricle to the pump.
- C. The proximal end of the outflow conduit is connected to the outflow port of the pump drive unit.
- D. Its distal end is anastomosed to the ascending aorta. The outflow conduit carries blood from the pump to the aorta.
- E. The percutaneous lead, containing the power and signal leads, exits from the right upper abdominal quadrant.

Implantation technique

A standard median sternotomy incision is performed with extension to the umbilicus. A pocket is created in the left abdominal wall, anterior to the posterior rectus sheath, between the costal margin and the iliac crest. The left anterior diaphragm is dissected to a point adjacent to the cardiac apex to allow for the inflow cannula route.

Cardiopulmonary bypass is initiated and heart failure surgery is performed.

The assist device is assembled. Using the provided trocar the percutaneous lead is tunnelled through the right upper quadrant of the abdominal wall.

The provided apical cuff is sutured at the LV apex. A left ventriculotomy is performed centred within the apex as exposed through the apical cuff. The inflow cannula is inserted through the LV apical cuff into the LV. Proper positioning is confirmed, the inflow cannula is secured in place with heavy suture or umbilical tape tied around the LV apical cuff, through which the inflow cannula has been passed. The left ventricle and the assist device are allowed to fill with blood.

The outflow conduit is trimmed to the correct length. The outflow graft strain relief and the flow

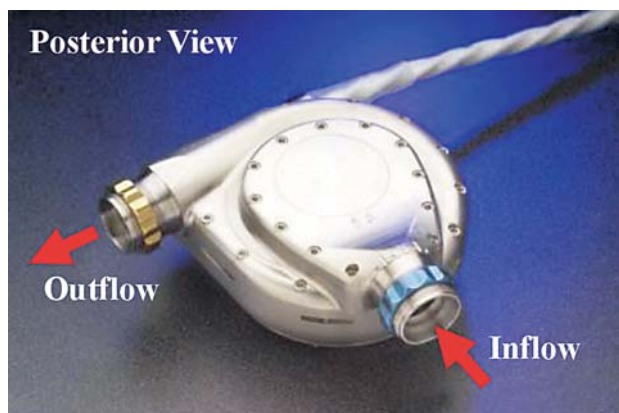


Figure 3. The pump drive unit. Posterior view of the smooth titanium housing of the pump drive unit. The inflow and outflow ports are shown. The percutaneous lead is assembled to the pump drive unit.

probe are placed over the outflow graft. An end-to-side anastomosis is performed to the anterolateral portion of the ascending aorta. The pump is started and run at a low speed to facilitate the de-airing process. Once de-airing is complete, the clamp is released from the outflow graft and the pump's speed is slowly increased during weaning from cardiopulmonary bypass.

Patient selection

To be enrolled in the study candidates must meet inclusion and exclusion criteria, but the decision to use the LVAD is ultimately made on an individual basis after careful evaluation of the short and long-term risks and benefits to the patient and consideration of alternative methods of treatment.

Enrolment and treatment of the first patient

Three patients with end-stage heart failure were initially evaluated for WorldHeart Rotary Pump implantation as a bridge to recovery after heart failure surgery. All three patients had continuing decompensation of heart failure despite optimal medical treatment, with deteriorating haemodynamic condition and increasing risk of death.

One of the three candidates unfortunately died of heart failure a few weeks before final evaluation and before the initiation of the study. Both of the two remaining candidates were suitable for the WorldHeart Rotary Pump implantation according to inclusion and exclusion criteria. In one of them, with ischaemic car-

diomyopathy, left ventricular recovery was considered highly unpredictable and a Novacor LVAD was implanted as a bridge to recovery, or alternatively as a destination therapy.

The first patient enrolled in the study was a 67-year-old male with a long history of progressively deteriorating idiopathic dilated cardiomyopathy, with severe functional mitral valve regurgitation and symptoms of NYHA class IV heart failure for several months before enrolment, despite medical treatment. In addition he had a recently developed 50% stenosis of the left anterior descending artery. He also had a permanent VDD pacemaker (Pulsar 870, Guidant) implanted because of complete atrioventricular block.

The standard transthoracic echocardiogram (Phillips Sonos 7500) and the real-time three-dimensional echocardiogram¹ (Sonos Phillips 7500, 'Live 3D') demonstrated severe dilatation of the left ventricle, with globally reduced LV function, a severe central jet of functional mitral regurgitation, and significant global dyssynchrony. The right ventricle, on the other hand, was not dilated and showed adequate excursion of the free wall with only mild to moderate tricuspid regurgitation.

The patient underwent aortocoronary bypass grafting with a skeletonised, pedicled LIMA graft to the left anterior descending branch, undersized mitral valvuloplasty with a 26 mm Geoform Edwards Lifesciences ring, implantation of an epicardial screwing lead (EnPath 511211, Guidant) at the lateral LV wall and implantation of the WorldHeart Rotary Pump LVAD.

In the postoperative period, apart from unloading the left ventricle with the LVAD, pharmacologic agents known to induce reverse remodelling (such as β -blockers, angiotensin-converting enzyme inhibitors, and spironolactone)¹ are used, and cardiac resynchronisation therapy was started.

Discussion

In the present study the first human implantation of a new, continuous-flow LVAD, the WorldHeart Rotary Pump (WorldHeart Inc., Oakland CA), is presented. The unique hypothesis of this study is that reparative heart failure surgery combined with postoperative mechanical support, ventricular resynchronisation where indicated, and optimisation of the pharmacological treatment can maximise myocardial recovery.

Heart transplantation is the gold standard of surgical treatment for selected patients with end-stage

heart disease. However, it is applicable only to a small number of patients.³¹ In an effort to address this problem, alternative surgical approaches are evolving, including mitral valve annuloplasty, left ventricular remodeling surgery³² and left ventricular mechanical support.^{1,2}

Severe mitral regurgitation is a frequent complication of end-stage cardiomyopathy, significantly contributing to the progression of heart failure and predicting poor survival.³² It has been suggested that for patients with end-stage cardiomyopathy and severe mitral regurgitation, mitral valve reconstruction as opposed to replacement may improve symptoms and survival. Bolling et al reported very good immediate and mid-term results with implantation of an undersized annuloplasty ring (with concomitant coronary bypass grafting for incidental coronary disease and tricuspid valve reconstruction for severe tricuspid regurgitation).³³ Akar et al³⁴ and Tavakoli et al³⁵ summarised the favourable clinical results of mitral valve repair surgery in ischaemic mitral regurgitation.

In patients with ischaemic cardiomyopathy, not only the amount of viable myocardium but also the extent of left ventricular remodelling determines the outcome following myocardial revascularisation. Patients with a high end systolic volume have a decreased likelihood of improvement of cardiac function.^{36,37} In these patients good results have been reported with ventricular surgical remodelling combined with coronary grafting and valvular reconstruction.³⁸⁻⁴¹ The goals of the procedure are to revascularise wherever possible, and to restore the size and shape of the LV.^{32,42} Good results with this approach have also been reported in patients with non ischaemic cardiomyopathy.⁴²

Mechanical bridge to left ventricular recovery is an emerging strategy for the treatment of heart failure and device-based approaches should inspire research to find ways to make recovery more complete and permanent.²

In our early experience with a percutaneously inserted LVAD,⁴³ even short-term post-cardiotomy support after left ventricular surgical geometric remodelling, usually with concomitant revascularisation and mitral valve repair, yielded good results. The major indication for the LVAD insertion was failure to wean from cardiopulmonary bypass, and the maximum duration of support was eleven days. Despite the well established indication for Intra-aortic Balloon Pump (IABP) insertion as the first

means of treatment in acute heart failure not amenable to medical treatment,⁴⁴ in these patients with acute perioperative decompensation of chronic heart failure mechanical support was generally not preceded by IABP insertion. The reparative heart failure surgery induced surgical remodelling and although the short period of post-cardiotomy support did not allow reverse remodelling, it allowed the heart to recover from the operative insult. Even though all 6 patients were weaned from the device, heart failure reoccurred in 2 of them within 3 months postoperatively. We thought that these patients could benefit from longer periods of support. Thus the idea of mechanical support after heart failure surgery as a bridge to recovery was born.

The new implantable pump will provide left ventricular mechanical support as a bridge to recovery, supplemented with pharmacological treatment that promotes reverse remodelling, and resynchronisation therapy when needed.

Myocardial recovery induced by LVADs is considered best served by apical rather than atrial cannulation.^{17,45} The WorldHeart Rotary Pump is an LVAD implanted with apical cannulation and could provide sufficient unloading of the LV.

Simon et al²⁸ suggested that recovery of function was an early phenomenon that occurred within 2 months of LVAD support. Farrar et al²¹ suggested that 50 days of left ventricular support would capture half the patients who would ultimately recover ventricular function followed by successful device removal. Madigan et al²⁹ indicated that maximum structural reverse remodelling of the heart by LVADs is complete by about 40 days. Even though recovery has been reported even after 1 to 26 months of support,^{10,11,17} it has also been suggested that after the point where maximum recovery is reached no further improvement can be anticipated and lasting recovery seems to be related to a more rapid restoration of normal heart function initially after assist device implantation.¹⁷ Therefore, a maximum period of support of 30-90 days seems adequate to capture those patients in whom lasting recovery can be anticipated.

Postoperative mechanical support could allow non-transplant reparative heart failure surgery in the subgroup of patients with high anticipated early mortality. We hypothesised that a combination of techniques could increase the low incidence of myocardial recovery²⁴ after LVAD implantation in patients with chronic heart failure. The strategy of combining treatments to reverse

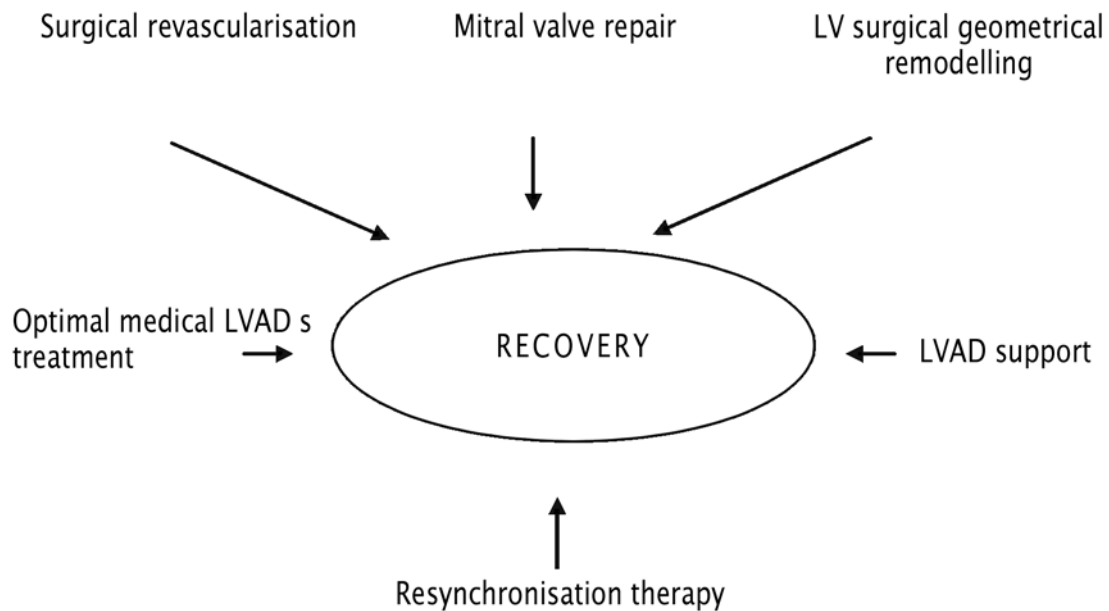


Figure 4. End-stage heart failure treatment: a multidisciplinary approach. LV-left ventricle; LVAD-left ventricular assist device.

the LV pathology could yield better results than any of these treatments alone. Individually tailored treatment, including repair of the mitral valve, surgical remodelling of the LV and revascularisation when indicated, followed by unloading the LV by mechanical support, medical treatment to promote reverse remodelling and resynchronisation therapy when indicated, could increase the likelihood of recovery (Figure 4).

Our first patient had end-stage heart failure not amenable to medical treatment and he was not a candidate for transplantation. Non-transplant heart failure surgery seemed to be the only alternative. A global therapeutic approach was adopted in order to address the different aspects of his cardiac pathology.

The preliminary results are very encouraging. The support period was free of serious adverse events. Weaning from the device was successful, and functional myocardial recovery after device explantation was achieved. Upon completion of the study valuable information will be yielded not only about the feasibility of implantation of the Worldheart Rotary Pump in human, but also about recovery of the failing myocardium.

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