Advanced heart failure: feasibility study of long-term continuous axial flow pump support

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Aims A lack of donor hearts has stimulated interest in using blood pumps to treat severe heart failure. We tested the hypothesis that a new continuous flow circulatory assist device could be employed safely to relieve symptoms of heart failure and evaluated the potential to prolong life.

Methods and results An intracardiac axial flow pump was implanted in 17 heart failure patients [idiopathic dilated (12), ischaemic (4), or amyloid cardiomyopathy (1)]. All were deemed ineligible for transplantation. Implantation of the device was by left thoracotomy (15) or median sternotomy (2). Power delivery was by a skull-mounted titanium pedestal. All patients survived surgery. None needed right ventricular support. There were three hospital deaths, two early from subdural haematoma and aortic thrombosis, one late after switching to transplantation. A total of 14 patients left hospital with a cumulative support-time of 15.9 years (median: 293 days, interquartile range: 286 days, 1–44 months). Actuarial 1-, 2-, and 3-year survivals were 56, 47, and 24%, respectively. There was no pump failure. Quality of life scores improved. Two superficial pedestal infections were successfully treated. Four patients had cerebral thrombo-embolism: two early events attributed to inadequate anticoagulation and two late with near-complete resolution. An improved anticoagulant regime addressed this problem. Late death occurred in five patients from battery disconnection, subdural haematoma, bowel ischaemia, respiratory failure, and after cardiac transplantation.

Conclusion Continuous flow blood pumps provided symptomatic relief of severe heart failure with high quality of life. Event-free survival reached 4 years. Analysis of adverse events led to improved management strategies. There is potential for widespread use of blood pumps in the community. A controlled trial is required.
Introduction

Although cardiac transplantation provides the optimum treatment for advanced heart failure in a small number of patients, the recent decline in organ donation contrasts starkly with the increasing number of suitable patients. This therapeutic void might be filled by the extended use of left ventricular assist devices (LVADS) as lifetime treatment for those without access to a donor heart. The control patients in the Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) study defined the dismal outlook for these patients. Although both longevity and quality of life were limited by complications of the ‘first generation’ pulsatile LVAD, the REMATCH study set the precedent for long-term circulatory support in selected patients who face impending death.

Evolving blood pump technology has led to the manufacture of LVADS with improved safety and durability. This, together with the propensity for native heart function to improve with unloading, has influenced patients to request an LVAD in preference to the unpredictability of the transplant waiting list. Until recently, pulse pressure was thought to be necessary for recovery of end organ function and long-term cardiovascular homeostasis. Although continuous flow pumps can be constructed in much smaller form and with fewer parts subject to mechanical failure, the safety of indefinite continuous flow circulatory support remains unknown. After comprehensive pre-clinical testing of the Jarvik 2000 in Houston and Oxford, we reported the first permanent implant of a continuous flow pump in the Lancet in 2000. Four years later, this patient continues to live an active and productive life without any device-related complications.

Since the report, a collaborative feasibility study of ‘lifetime treatment’ has been carried out in selected non-transplant eligible patients in the UK and Germany. Prior to this report there have been no long term safety and efficacy studies with continuous flow pumps and these devices have yet to be approved for indefinite use in the USA.

We performed this feasibility study in advance of a proposed prospective randomized trial of continuous flow pumps vs. medical management. To address the life-threatening problem of percutaneous drive line infection, we used a skull pedestal power delivery system based on techniques for artificial hearing. With this approach, all the vulnerable external elements of the power and control system are exchangeable.

Methods

The Jarvik 2000 pumping mechanism and novel power delivery system have been described previously. This compact device is implanted within the cavity of the failing left ventricle via the apex. Internal and external power lines connect at the skull pedestal are shown in Figure 1. Rechargeable external batteries are attached to the controller and provide power for up to 8 h. The external components are easily portable on a belt or shoulder bag. The impeller rotates at 8000–12 000 r.p.m. delivering between 3 and 6 L of blood flood per min depending on afterload. The device is currently approved for clinical investigation only. The study protocols for ‘intention to treat by lifetime LVAD support’ were approved by the ethical committees of each participating centre and the regulatory authorities of each country. In the UK, we decided to concentrate on patients with idiopathic dilated cardiomyopathy.

Patient selection

A list of all inclusion and exclusion criteria is given in Table 1. All patients had been fully assessed but deemed unsuitable for cardiac transplantation at the time of recruitment. Criteria that made the patients ineligible for transplantation at the time of presentation were elevated pulmonary vascular resistance (seven), age (six), amyloidosis (one), and patient request (two). One patient with a small body size (1.5 m²) was too ill for transplantation and needed mechanical circulatory assistance.

Between March 2000 and February 2004, 16 male and 1 female patient aged 49–74 years were enrolled in the study. The number of patients was limited by financial constraints. In the UK, the device cost £60 000 and hospital fees ranged from £28 000 to £200 000. Table 2 lists patient demographics and pre-operative haemodynamic data. All but one patient had either
idiopathic-dilated cardiomyopathy or ischaemic cardiomyopathy with chronic heart failure (NYHA IV) despite maximum medical management. One patient had severe diastolic heart failure due to myocardial amyloidosis. Also, the patient had a maximal oxygen uptake of 7 mL/kg/min with a small, thick-walled ventricle, and an ejection fraction of 40%. Each patient was judged to have sufficient family support in the event of an LVAD complication occurring at home. Two patients were receiving intravenous inotropes at the time of surgery.

Although exclusion criteria included raised pulmonary vascular resistance (PVR > 7 Wood units), the female patient reported a PVR of 10 Wood units due to endstage ischaemic cardiomyopathy. After previous coronary bypass surgery, there were no further treatment options and she received the device with ethics committee approval on compassionate grounds outside the study protocol.

### Surgical methods

In 15 patients, the device was implanted through a sixth intercostal space left thoracotomy which provided access to the left ventricular apex and descending thoracic aorta. Two patients underwent median sternotomy, one for concomitant coronary artery bypass and the other to avoid thoracotomy after recent empyema drainage and lung resection.

### Device management and follow-up

Details of post-operative care have been provided elsewhere. With an impeller speed between 10 000 and 11 000 r.p.m, pulse pressure was diminished or completely absent in the early post-operative period. Anticoagulation with warfarin aimed to achieve an International Normalized Ratio (INR) between 2.5 and 3.5. In Germany, aspirin 80 mg/day was added to this regime part way through the study. ACE inhibition, beta blockade, or both, were continued to optimize pump flow by lowering systemic vascular resistance. The LVAD provided between 3 and 5 L of blood flow against a mean blood pressure of 70–90 mmHg. Partial left ventricular unloading allowed opening of the aortic valve, washing of the aortic root, and probably better coronary flow. Some patients increased their pump speed to 11 000 or 12 000 r.p.m. during exercise.

The patients and their close relatives were taught to use the controller, replace and recharge the batteries, and exchange the external components in the event of malfunction. Patients were discharged between 3 and 8 weeks post-operatively. In Germany, patients attended a rehabilitation centre for a structured exercise program before returning home.

Each patient was reviewed electively as an outpatient every 6–8 weeks. Functional status was determined and quality of life assessed with the Minnesota ‘Living with Heart Failure’ questionnaire at 3, 6, and 12 months after surgery. For patients, who were unable to perform the follow-up questionnaire at 3 months, a value of 100, equal to the highest score measured pre-operatively, was assumed for statistical analysis, in order to correct for selection bias.

All patients had an echocardiogram to assess native heart function and rule out thrombus formation within the heart or graft. Any device-related complications were noted. The external cable was detached from the skull pedestal, the site inspected for infection and cleaned.

Multiple exchanges of external cables and batteries were undertaken in response to wear and tear. In the event of a serious complication, a re-evaluation for transplantation was performed. If the patient had significant improvement in renal status or a lowering of pulmonary vascular resistance, they were listed at that point.

### Statistical analysis

Data is presented as mean values ± SD for quantitative variables, time variables are presented as median values with interquartile range (IQR). Changes in quality of life scores
were tested by means of the Wilcoxon rank-sum test. All significance tests were two-sided and a $P$-value of $<0.05$ was considered to indicate statistical significance. Data analysis was performed using Instat 3 software (GraphPad Software, Inc., San Diego, CA, USA).

### Results

#### Post-operative morbidity and mortality

The first patient with biventricular failure, hepatic dysfunction, and ascites required surgical re-entry for bleeding but recovered well. He was the only patient with this complication (re-exploration rate 5.8%). After initial recovery, the second patient developed an extradural haematoma related to skull pedestal implantation following oral anticoagulation. He required prolonged ventilation after intracranial surgery and died from multi-organ failure 12 weeks post-operatively. Throughout this period, he was not anticoagulated. After this, careful skull thickness measurements were made in all patients and the skull pedestal instrumentation was modified. Another patient who was inadequately anticoagulated (aPTT 34 s) suffered ventricular fibrillation on post-operative day 7 due to thrombosis of his aortic root. Resuscitation resulted in fatal cerebral thromboembolism. These early events have not recurred after adjusting our treatment regimen. The remaining 15 patients left the intensive care unit between 4 and 30 days post-operatively (median: 8 days, IQR: 7 days).

One patient with a dilated ascending aorta (4.6 cm) and peripheral vascular disease suffered retrograde dissection of the descending aorta from the femoral artery cannulation site. To avoid bleeding, anticoagulation was delayed and he suffered an embolic stroke. He was discharged to a chronic care facility where he remains well with normal speech but has a motor disability. Another large patient (body surface area: 2.3 m$^2$) was never discharged from the hospital. His ischaemic left ventricle did not improve and he had persistent heart failure symptoms. The non-pulsatile pump was electively exchanged for a HeartMate VE LVAD (Thoratec Corporation, Pleasanton, CA, USA). Soon afterwards, this LVAD became infected. As the pulmonary vascular resistance had fallen, an urgent cardiac transplant was performed but he died from multi-organ failure 363 days after the first operation.

A total of 14 patients left hospital between 3 and 8 weeks post-operatively (median: 42 days, IQR: 15.5 days).

### Survival and late clinical events

The first patient in the series remains fully active, travels internationally, and is employed raising funds for the UK programme 4 years after his operation. Two life-threatening episodes of *Staphylococcus aureus* septicaemia, which occurred after nose bleeding, have not caused device infection.

The cumulative support time for all hospital survivors is 15.9 years (median: 293 days, IQR: 286 days) with a range between 1 and 44 months. Actuarial survival for the study group is shown in Figure 2. There were five late deaths (Figure 3) in the hospital survivors. In the UK, the 74-year-old patient died unexpectedly at home 1 year after implantation. Death followed a fall which caused an extra-dural haematoma contra lateral to the skull pedestal. Anticoagulation was a contributing factor, but he required this for chronic atrial fibrillation irrespective of the LVAD. A second patient died at 3 years from respiratory failure. Autopsy showed chronic obstructive airways disease and bullous emphysema. Apart from exchanges of the external power cable, none of these patients suffered any device-related complication. To date, there has been no LVAD infection or thromboembolism in any of the six UK patients.

One German patient developed a superficial skull pedestal infection at 230 days. This cleared after antibiotic treatment but was followed by recurring heart failure symptoms due to partial thrombosis at the outflow bearing. Because his pulmonary vascular resistance had fallen during LVAD support, he was transplanted electively but died from pseudomonas infection 3 days later. The patient with myocardial amyloidosis was found dead at home with the battery disconnected. This problem of absolute pump dependence was addressed by developing a Y-cable connector so that the system need not be disconnected from a battery at any time.
A third patient with chronic occlusion of the celiac and inferior mesenteric arteries suffered an intestinal bleed. Colectomy was required for bowel infarction but he eventually died from multi-organ failure. A fourth patient with idiopathic-dilated cardiomyopathy and no ventricular recovery developed biventricular failure 12 months after implantation. After improvement in renal function during 385 days of LVAD support, he was transplanted and remains well.

Two other patients had late transient neurological events presumed to be embolic in origin. This problem was addressed by increasing the INR to between 3.0 and 3.5 and adding aspirin 80 mg daily. One of these patients then developed a late *S. aureus* skull pedestal infection which was controlled with oral antibiotic treatment.

Although external components of the system have been exchanged in response to wear or accident, there has not been any mechanical failure of the implantable parts during a cumulative support time in all implanted patients of 5996 days (16.4 years).

**Autopsy studies**

All six patients who died with the device *in situ* had detailed autopsy with participation of the implanting surgeons. Care was taken to dissect out the pump with power cables intact so that the system could be returned to the manufacturer for bench testing and durability studies. After implant times between 3 months and 3 years and even in the absence of anticoagulation...
(second UK patient) each pump and vascular graft was free from thrombus. A tiny ring of denatured protein was found inseparable from, but not interfering with, the inflow bearing. There was no thrombus around the pump inflow within the left ventricle and no injury to the mitral subvalvar apparatus. The aortic valve cusps did not show any sign of fusion as may occur with pulsatile LVADS which actively empty the left ventricle and never allow the aortic valve to open. There were no embolic infarcts in the kidneys, spleen or liver of any of the patients. One small old infarct was found in the brain of the patient who died from chronic obstructive pulmonary disease. This patient also had gross right ventricular dilatation and tricuspid insufficiency. In idiopathic dilated cardiomyopathy patients, myocardial histology was compatible with some reverse remodelling. The titanium skull pedestal was removed and the site inspected. All pedestals were firmly healed in place and without bone or skin infection. All implanted cables were free from infection though the inflammatory adhesions around the apical cuff and vascular graft suggested that re-operation for pump exchange would be extremely difficult.

Quality of life
Preoperative Minnesota Quality of Life Score ranged from 33 to 100 (mean: 72 ± 21). Two patients with scores of 33 and 36 were in denial of their condition. This was documented pre-operatively by a psychologist and illustrated by an MVO$_2$ of 8 and 9 mL/kg/min, respectively, and inability to walk more than a few steps. Pre- and post-operative Minnesota ‘Living with Heart Failure’ scores are presented in Figure 4. Quality of life at 3 months after surgery was significantly improved ($P = 0.0015$). Even if a value of 100, equal to the highest value measured in any patient pre-operatively, was assumed for those unable to take the test at 3 months in order to correct for a selection bias, the difference remained significant ($P = 0.0302$). This compact intracardiac device was user friendly with no sensation from the implanted components. The external components were inobtrusive, easily portable, and simple to use. Patients were able to take a shower, but not swim. Unrestricted life in the community included long haul international air travel and vigorous activity experienced in farm work, dancing, or skiing.

Discussion
This is the first study to demonstrate the safety and efficacy of long-term continuous flow pumps which, in contrast to first generation LVADS, reduce stroke volume, and pulse pressure. Unlike donor hearts, mechanical blood pumps are an unrestricted commodity. After REMATCH, 67 centres in the USA are performing permanent implants of the Thermo Cardio Systems ‘Heart Mate’ LVAD. Currently, 30 bioengineering groups worldwide are involved in the development of miniaturized LVADS to provide independence from the hospital and an unrestricted, high-quality lifestyle. After leaving hospital, device-related infection and late mechanical failure were the leading causes of death in the REMATCH study. The Jarvik 2000 has minimized the risk of these complications. Skull pedestal infection is infrequent, remains localized and does not reach the pump itself. Although the exchangeable external parts are subject to wear and tear, there has been no mechanical failure of the implantable components. The thrombo-embolic complications in ischaemic patients have been addressed by modifications in pump and controller design and improved anticoagulation. Freedom from death or device-related complications are
competitive with the REMATCH trial and we recorded excellent quality of life scores. This is encouraging given the difficulties in managing continuous flow circulation and the challenge of the new surgical techniques.

Not all patients were free from heart failure symptoms. In contrast to the pusher plate LVADS which empty and completely replace the left ventricle, the axial flow pumps are best used to assist native heart function. At autopsy, there were no ultrastructural changes in other organs which might contraindicate long-term non-pulsatile blood flow, but we are examining changes in aortic wall morphology. Exercise increases total blood flow by physiological mechanisms, although higher pump speeds may be used by those whose native ventricular function does not improve.

There are informative differences between the UK and German experience. The UK approach was to implant the device in severely symptomatic but ambulatory patients with idiopathic-dilated cardiomyopathy before deterioration into cardiogenic shock. Perhaps because of this, there were less complications than in terminally ill, hospital bound German patients who were unsuitable for transplantation. Several of these had atherosclerotic cardiovascular disease with scarred hearts beyond the stage which could improve with mechanical unloading. Accordingly, the long-term durability and safety of this pump argue for earlier implantation. Synergy then develops between the LVAD and native heart function which appears to promote prolonged event-free survival. We, like others, have observed some functional improvement or stabilization in the myocardium of dilated cardiomyopathy patients. Earlier unloading before extensive fibrotic change may further increase the likelihood of recovery. When the aortic valve remains permanently closed, there is the risk of turbulence and stasis in the aortic root. This may predispose to thrombosis in the aortic sinuses or at high-grade coronary stenoses particularly if anticoagulation is inadequate. We believe that dyskinetic myocardial scar and stasis in the aortic root are more likely to generate thrombo-embolism than the pump itself. This could explain the higher incidence of thrombo-embolism in German patients as there were no ischaemic patients in the UK cohort.

The non-transplant eligible chronic heart failure cases are more difficult to rehabilitate than younger bridge to transplant patients with acute heart failure. Consequently, it is significant that our first candidate has remained complication-free on continuous flow support for a period similar to that of the longest surviving pulsatile LVAD patient. We also consider that adverse events can be reduced further by improved patient selection, greater surgical experience, or more assiduous anticoagulation management particularly in ischaemic patients. Equally, we can no longer distinguish dogmatically between intention to treat by lifetime use or bridge to transplantation. Patients initially deemed unfit for transplantation can become eligible in response to left ventricular unloading and its effects on pulmonary vascular resistance or renal function. Paradoxically, some patients who had improved sufficiently to fit transplant selection criteria had excellent quality of life with the LVAD and were unwilling to consider further surgery.

The difficulties conducting clinical trials with mechanical assist devices for patients with life-threatening heart failure have been outlined in a recent consensus conference, where the pivotal role of multicenter clinical registries has been emphasized. The second annual report of the International Society for Heart and Lung Transplantation (ISHLT) database of mechanical circulatory support devices has been recently published. One year survival rates in destination therapy patients were 29%, as opposed to 56% in our series. In addition, we reported post-transplant outcomes with our survival data, whereas in the ISHLT database survival was censored at the time of transplantation. Without post-transplant outcomes 1-year survival rates in our series would have been 74%. Such a multicenter registry advances both risk stratification for outcome prediction and the development of a multivariate regression model to help adjust for differences between cohorts, even if the drawbacks of voluntary data reporting are considered. A greater confidence in our ability to identify high-risk populations could sharpen future trial design by streamlining better selection of target populations and better prediction of event rates. In addition, it could accelerate recognition of devices with breakthrough results, even in the absence of randomized controlled trials.

In summary, this study shows that a miniaturized continuous flow device can be used for long-term treatment of advanced heart failure with safety and efficacy. It remains difficult to achieve exemplary results in non-transplant eligible chronic heart failure patients with end organ dysfunction. To improve on this situation, lifetime LVAD implants should be performed only on an elective basis and preferably in a controlled trial. Circulatory support then has similar therapeutic potential to haemodialysis in renal failure which provides a 60% chance of 2-year survival.

We now plan a prospective randomized trial of continuous flow LVADS vs. continued medical treatment in ambulatory patients (NYHA III or IV before the terminal stage) who are unsuitable for transplant or decline this option.

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