Jarvik 2000 Heart
Potential for Bridge to Myocyte Recovery

Stephen Westaby, MS, FRCS; Takahiro Katsumata, MD, PhD; Remi Houel, MD; Rhys Evans, MD; David Pigott, MD; O.H. Frazier, MD; Robert Jarvik, MD

Background—Mechanical bridge to left ventricular recovery is an emerging strategy for the treatment of heart failure. We sought to validate the use of a new intracardiac axial flow impeller pump for this purpose.

Methods and Results—The Jarvik 2000 Heart was implanted into 30 sheep to ascertain mechanical reliability, biocompatibility, and hemodynamic function. We attempted but failed to anticoagulate with warfarin. Elective explants with survival were performed in 3 animals to simulate bridge to recovery. Extensive autopsy studies were performed in all other animals. At speeds between 8000 and 12 000 rpm the device pumped up to 8 L/min, captured all mitral flow, and augmented cardiac output with elevation of mean arterial pressure. The pump was silent and hemolysis negligible. Nonpulsatile flow did not adversely affect neurological or renal function. Device removal proved straightforward and safe. A fractured inflow bearing occurred in 1 early model. There were no other pump failures, but power interruption occurred when the sheep chewed the cables or head-butted the percutaneous pedestal. At autopsy, there was no thromboembolism or primary thrombus formation in any device. Pump occlusion occurred in 2 sheep with bacterial endocarditis. One electively explanted pump, previously switched off for 5 months, had no thrombus in the device or vascular graft.

Conclusions—The Jarvik 2000 Heart is a major advance in blood-pump technology and increases the scope of mechanical circulatory support. Reliability and ease of removal favor its use for bridge to myocyte recovery, as well as for bridge to transplantation or long-term support. (Circulation. 1998;98:1568-1574.)

Key Words: heart failure ■ myocytes ■ Jarvik 2000 ■ heart-assist device

While the incidence of heart failure continues to rise, both medical and surgical treatment options remain limited. The radical solution, cardiac transplantation, is constrained by donor availability. The left ventricular reduction (Batista) operation remains controversial, and dynamic cardiomyoplasty seems ineffective. There is room for a new approach.

Recent experience from mechanical bridge to transplantation has provided compelling evidence for myocyte recovery after prolonged left ventricular unloading. Myocyte morphology and metabolism may return to normal in dilated cardiomyopathy, and recovery appears sustainable particularly after myocarditis. This has encouraged some centers to pursue mechanical bridge to myocyte recovery as an alternative to cardiac transplantation for selected patients. In this context the scope of existing left ventricular assist devices (LVADs) is limited by size, noise, and driveline problems, including infection, which restrict their use predominantly to adult males. Conducting an uneventful LVAD removal while preserving the native heart is difficult. In contrast, the emerging axial flow impeller pumps are compact and silent with the potential for ease of extraction.

Their mechanical function allows the process of weaning from the device. We have tested the feasibility of a mechanical device in this context using the Jarvik 2000 Heart. We assessed the relationships between pump flow, cardiac physiology, and the risk of hemolysis and also tested removal of the device with survival. An approach to avoid driveline infection using an innovative new percutaneous system is under study.

Methods

Jarvik 2000 Heart

The Jarvik 2000 Heart is a compact axial flow impeller pump with an outflow Dacron graft for anastomosis to the descending thoracic aorta (Figure 1). The pump is inserted through a sewing cuff into the apex of the left ventricle. The adult model measures 2.5 cm in diameter by 5.5 cm in length. The weight is 85 g with a displacement volume of 25 mL. The pediatric device measures 1.4 cm in diameter by 5 cm in length; the weight is 18 g, and the displacement volume is 5 mL. The pump rotor contains the permanent magnet of a brushless direct current motor and mounts the impeller blades. A titanium shell accommodates the rotor and suspends it at each end by tiny, blood-immersed ceramic bearings. The adult pump functions at speeds of 8000 to 12 000 rpm, providing blood flow up to 8 L/min. The smaller pediatric version pumps up to 3 L/min. Noise is imperceptible.
In the last 10 animals, the power cable with the Jarvik 2000 pump was implanted. The Dacron graft was first anastomosed end to side to the descending thoracic aorta. The pump was then inserted through a cuff sewn to the apex of the left ventricle. This was achieved by excising apical left ventricular muscle with a cork bore while the heart supported the circulation. Cardiopulmonary bypass was not required.

The percutaneous power cable was then connected to the external controller and battery or direct current main power supply.

**Intraoperative Hemodynamic Studies**

In the last 6 animals implanted with the definitive adult human model, an electromagnetic flow probe was placed around the graft to record flow during detailed hemodynamic studies.

Carotid arterial pressure, pulmonary wedge pressure, and graft flow were measured before and after insertion of the pump, then serially with escalating pump flow to the maximum speed tolerated before collapse of the left atrium. Measurements were made in triplicate and the average used to plot flow curves. The flow probe was removed before the chest was closed.

**Recovery**

At the end of the procedure a single chest drain was inserted, the chest closed, and the muscle relaxant reversed. The sheep were extubated after 30 to 60 minutes of spontaneous respiration with documentation of satisfactory blood gases and acid base balance.

A vest was placed around the thorax to carry the controller and connect with the overhead electrical power line. The animals were then allowed to mobilize, drink, feed, and roam around the sheep pen. Blood from uncrossmatched donor sheep was used to correct hypovolemia or anemia. Indwelling carotid arterial and jugular venous lines were left in situ in all animals for 48 hours. These were used to monitor arterial and venous pressure and to determine the rate of pump flow that abolished left ventricular ejection through the aortic valve. At this stage, all systemic blood flow was through the pump and was nonpulsatile. This flow rate was maintained, and the animals were observed for adverse neurological or renal effects of nonpulsatile flow. Neurological status was determined after recovery from anesthetic by observing behavior, mobility, and balance. Renal function was assessed by measurement of blood urea and creatinine; hydration was maintained by intravenous fluid administration.

After removal of the indwelling lines, blood samples were obtained by direct puncture of the internal jugular vein. Pump speed and power requirements were measured and recorded twice daily. Auscultation was used to check the tone of the device.

Aspirin 300 mg/d and warfarin in doses escalating to 25 mg/d were prescribed, but because of the sheep’s rumen, it proved impossible to achieve an International Normalized Ratio >1.5:1.

**Elective Device Removal**

To simulate the bridge to myocardial recovery strategy, permission was obtained from the Home Office to perform 3 elective device explants with survival. Animals chosen for elective explant had suffered irreparable power interruption, and the pumps were removed at 25, 198, and 211 days postoperatively. The animals were anesthetized and positioned for left thoracotomy; the medial one third of the healed thoracotomy wound was reopened. The apex of the heart was located by sharp dissection through dense adhesions, and the vascular graft was ligated and transected. The device was then removed by cutting the ligatures in the cuff and directly oversewing the apical window. No circulatory support or antidys-
TABLE 1. Complications

<table>
<thead>
<tr>
<th>Events</th>
<th>No. of Sheep</th>
</tr>
</thead>
<tbody>
<tr>
<td>Device-related</td>
<td></td>
</tr>
<tr>
<td>Pump failure (fractured bearing)</td>
<td>1</td>
</tr>
<tr>
<td>Thrombosis</td>
<td>0</td>
</tr>
<tr>
<td>Anticoagulation-related hemorrhage</td>
<td>3</td>
</tr>
<tr>
<td>Endocarditis</td>
<td>2</td>
</tr>
<tr>
<td>Driveline infection</td>
<td>2</td>
</tr>
<tr>
<td>Malhealing of the wound</td>
<td>5</td>
</tr>
<tr>
<td>Non–device related</td>
<td></td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>4</td>
</tr>
<tr>
<td>Respiratory infection</td>
<td>2</td>
</tr>
<tr>
<td>Sepsis</td>
<td>2</td>
</tr>
<tr>
<td>Interrupted power delivery</td>
<td>15</td>
</tr>
</tbody>
</table>

rhythmic therapy was used. The thoracotomy was then closed without a drain, and the sheep were allowed to recover.

Autopsy Studies
After death or elective euthanasia, the device was removed from the left ventricle, photographed, and disassembled, in a search for thrombus formation. The bearings and moving parts were checked for wear. The heart, lungs, brain, kidneys, and liver were examined for macroscopic evidence of thromboembolism. Slices of brain, heart, and kidney were examined histologically. The percutaneous pedestal and surrounding tissues were closely inspected for signs of infection.

Statistic Analysis
All results for continuous variables are expressed as mean±SD. Student’s paired or unpaired t test or Mann-Whitney U test, if appropriate, was used to compare continuous variables between 2 subgroups. A P value of <0.05 was considered indicative of statistical significance.

Results
Mortality and Morbidity
During the learning curve, 3 deaths occurred in the perioperative period as a result of ventricular arrhythmia caused by suturing or coring the heart. This complication was eliminated by infusing the antisyrrhythmic agent bretylium 30 minutes (rather than immediately) before apical coring. An additional 4 deaths occurred within 24 hours of the operation from inhalation and respiratory failure or intrapleural bleeding (aorta or internal mammary artery).

One animal developed acute mitral insufficiency during ventricular coring and was euthanized immediately. Autopsy showed a severed strut chord stuck in the inflow of the device. These events each occurred during our first 15 implants, reflecting the learning curve and our inexperience with the animal model.

Twenty-two animals survived between 3 and 198 days (mean 52±12 days) with a functioning device. All complications are annotated in Table 1.

Three sheep died of secondary hemorrhage from the aorta between the third and fifth postoperative days. They had initially made an uneventful postoperative recovery, but severe hypertension and bleeding were noted at the time of arterial line removal from neck. All 3 were found to be excessively heparinized pending attempted anticoagulation with warfarin. Two sheep in whom arterial cannulae were kept for several days contracted bacterial endocarditis. These animals had a persistent febrile illness from the first postoperative week and eventually developed pneumonia or sepsis. One died and the other one was euthanized, at 42 and 74 days respectively.

Driveline infection (n=2) and impaired healing of cable exit site (n=5) occurred in sheep with a mobile percutaneous power cable at the shoulder. In contrast, all 10 animals with skull-mounted pedestals were free from infection or healing problems.

Three sheep died suddenly at 13, 17, and 22 days, respectively, of delayed aortic rupture, not at the anastomosis but at the site of side-clamp application. This problem was addressed by obtaining younger sheep instead of elderly ewes discarded from breeding stock. One died of peritoneal bleeding after rumen puncture for the treatment of acute bloat. Bloat occurred when a general anesthetic was administered to correct a subcutaneous power-line disconnection due to head-butting by the sheep. Two animals who developed perihof abscess were euthanized.

Nine animals experienced 15 incidents of electrical driveline breakage. This was inevitable given the humane, unrestricted environment required by the Home Office. Power cables were chewed by sheep in neighboring pens, and the percutaneous carbon pedestal was shattered by head-butting. Whenever possible, power was reestablished by electrical repair (usually several hours after disruption).

In 1 animal, the pump stopped because of a fractured bearing. The pump was later removed surgically, and the animal recovered. The bearing design was modified to provide greater strength; scanning electron microscope screening of all bearings was instituted to ensure that no cracks were present at implant. No further bearing fractures have occurred.

Performance of the Jarvik 2000 Heart
In 27 animals with the adult device, pump speeds were set and maintained between 10 000 and 12 000 rpm, and pulse width–modulated speed control at 14 V (DC power) was used. This pump speed corresponds with an in vitro flow of 5 to 6 L per minute. Natural ventricular contraction provided a differential pressure load on the pump, and the torque load on the motor varied with pulse pressure. The mean energy consumption was 6.3±1.1 W (n=25) during intraoperative measurement (baseline*), 5.8±0.9 W (n=9; P=0.09*) at day 30, 6.2±1.2 W (n=6; P=0.71*) at day 60, and 6.9±1.0 W (n=3) at day 90.

The 3 pediatric devices, which provided blood flow of 1 to 2 L/min, required 5 to 8 W at a continuous speed of 12 000 rpm and were operated at 8 to 9 V (DC).

Intraoperative Hemodynamic Studies
Introduction of the space-occupying (25-mL) device into the small, restrictive left ventricle of the sheep (with the vascular graft clamped) caused significant elevation of the pulmonary wedge pressure (8.0±0.6 mm Hg before implantation to 14.0±3.8 mm Hg after pump insertion, P=0.02). Before the
pump was switched on (clamp off the graft) there was bidirectional (to and fro) flow in the vascular graft but a mean negative (descending aorta to left ventricle) flow of 0.9±0.4 L/min corresponding to 21% of the total cardiac output (4.3±0.5 L/min). With “functional aortic regurgitation,” the pulmonary wedge pressure rose from 14.0±3.8 to 25.0±6.9 mm Hg (P<0.01), with a corresponding decrease in overall cardiac output from 5.1±0.7 to 4.3±0.5 L/min (P=0.01). Despite preexisting elevation of the left atrial pressure, this change in hemodynamics was well tolerated by the animals.

As the nonpulsatile pump flow increased, the aortic pulse pressure fell progressively from 25±4 (pump off) to 11±4 mm Hg at 10 000 rpm (P=0.06) (Figure 2). At 10 000 rpm, the pump captured all blood flow through the mitral valve so that the aortic valve remained in the closed position with the left ventricle fully unloaded. Systemic vascular resistance averaged 1190±170 dyne · s/cm. As the pump speed and flow rate increased further, the mean arterial pressure rose progressively, and at 12 000 rpm the cardiac output was augmented by 33% (1.9±0.5 L/min) over preimplantation values (Figure 3). At speeds exceeding 15 000 rpm, the left atrium became concave or collapsed, depending on the blood volume. Transfusion lessened this effect and allowed higher pump speeds and cardiac output.

**Effects of Nonpulsatile Flow**

With relatively simple neurological observation and measurements of urea and creatinine, we could detect no adverse sequelae from nonpulsatile flow. The animals’ behavior was normal with early restoration of feeding and drinking. There were no problems with balance after recovery from the anesthetic drugs. Renal function remained normal throughout.

**Hemolysis**

Table 2 shows indices of hemolysis preoperatively and at 1, 4, 8, 12, and 28 weeks.

Elevations of lactate dehydrogenase from 487±108 to 978±226 U/L (P=0.0001) at 1 week after operation probably resulted from uncrossmatched blood transfusion, drug administration, or resolution of intrathoracic hematoma after operation. Elevated levels of mean plasma-free hemoglobin from 11.5±8.7 to 14.2±7.7 mg/dL at 1 week were not statistically significant (P=0.55), nor were decreased hemoglobin levels (from 13.2±1.8 to 10.5±1.8 g/dL; P=0.14). Creatinine levels remained within the control range.

**Elective Explants**

All 3 animals recovered rapidly after limited thoracotomy and device removal to simulate bridge to left ventricular recovery. None required blood transfusion.

**Autopsy Studies**

There was no left ventricular endothelial overgrowth or intracavity thrombus formation. The most common findings were of pulmonary atelectasis and pleural effusion (n=12). Four animals had diffuse consolidation in the left lung. Histological examination showed chronic inflammatory changes with active bacterial infection.

Pump infection (endocarditis) was observed in 2 animals, 1 of which had excavating driveline sepsis. Both had a mass of vegetations around the inflow cage, which partially obstructed the pump head. One had extensive involvement of intracardiac structures, with mitral chordal fusion and septic embolism of the kidneys.

![Figure 2. Systemic arterial pressure and pump speed. As pump speed increased, mean arterial pressure progressively rose and pulse pressure diminished.](image-url-1)

**Figure 2.** Systemic arterial pressure and pump speed. As pump speed increased, mean arterial pressure progressively rose and pulse pressure diminished.

![Figure 3. Cardiac output and pump speed. At 10 000 rpm the pump captured all transmitral blood flow and the aortic valve remained closed. Cardiac output was determined by thermodilution. Flow through the vascular graft (conduit) was obtained by electromagnetic flowmeter. *(P<0.05).](image-url-2)

**Figure 3.** Cardiac output and pump speed. At 10 000 rpm the pump captured all transmitral blood flow and the aortic valve remained closed. Cardiac output was determined by thermodilution. Flow through the vascular graft (conduit) was obtained by electromagnetic flowmeter.
No abnormalities were detected in the brain or liver in any animal. In extensive (5-mm) histological sections of the kidneys from 10 noninfected animals that survived for >30 days, we found no evidence of thromboembolism, infarction, or infection.

In the 11 animals that survived >1 month with a functioning device, a tiny undetachable black ring torus (<1 mm) of heat-coagulated protein, fibrin, and degenerated platelets was found on the bearing supporting each end of the rotor (Figure 4). This did not restrict the rotation of the impeller or obstruct the inflow of the device. There was no increase in size of this nodule with time. There were no histological changes in the myocardium around the device that might suggest dissemination of heat into the tissues.

Apart from those with endocarditis, all pumps were remarkably free from thrombus formation even when disconnected from power for prolonged periods. After the device was removed, examination of the bearings showed no perceptible wear. One of the pumps electively explanted 5 months after losing power was free from thrombus with a completely clean vascular graft and no anticoagulation. In sheep in which devices stopped and were restarted several hours later, there were no detectable emboli or clinical events to suggest embolism.

**Discussion**

In contrast to the electric pusher-plate LVADs, the compact Jarvik 2000 Heart is silent, easily implantable, and unobtrusive. The intraventricular position conveys distinct advantages. The device is practically encapsulated by the native myocardium, and, theoretically, infections around the device may be less likely. There is no inflow graft at risk for thrombus formation, there are no valves, and the device can be used in patients of all sizes. Energy requirements are less than those of pusher-plate pumps, and the infection-resistant percutaneous electric cable has the advantages of simplicity and reliability. None of the animals with a skull-mounted carbon or titanium pedestal had driveline infection or impaired healing. A similar skull-mounted pedestal used for cochlear stimulation has functioned in humans for almost 20 years without causing infection.

The critical feature of the Jarvik 2000 design is a high-flow stream of blood that continuously washes the tiny bearings and prevents thrombus formation. Given the failure to achieve anticoagulation in normal sheep, the absence of thrombosis together with minimal hemolysis generates optimism for use in humans. In the electively explanted devices (with sheep survival), the pumps had been off for several hours or days without achieving anticoagulation, and still no thrombus occurred in the pump. Our findings are supported by the absence of thrombus formation or embolism in the animal experiments by Kaplon et al17 (sheep at the Columbia-Presbyterian Medical Center, New York, NY) and Macris et al18 (calves at the Texas Heart Institute). Collectively, these studies and the most recent work at the Texas Heart Institute have demonstrated mechanical reliability, remarkably little hemolysis, and freedom from thrombosis for up to 8 months after implantation. The tiny microtorus of coagulated protein on the bearings was not detachable, did not interfere with the moving parts, and is probably caused by local heat during high-speed flow.

It is now clear that moribund heart-failure patients fitted with an LVAD can improve to NYHA class I status and

<table>
<thead>
<tr>
<th>TABLE 2. Indices of Hemolysis</th>
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<tbody>
<tr>
<td>Before Operation</td>
</tr>
<tr>
<td>Hb (g/dL)</td>
</tr>
<tr>
<td>Pl-Hb (mg/dL)</td>
</tr>
<tr>
<td>LDH (U/L)</td>
</tr>
<tr>
<td>Cr (μmol/L)</td>
</tr>
</tbody>
</table>

Data presented are mean±SD. Cr indicates serum creatinine; Hb, hemoglobin; LDH, lactate dehydrogenase; and Pl-Hb, plasma-free hemoglobin.
Many patients between the ages of 60 and 75 given conventional medical treatment have an expected mortality of ≈40% per year. This is a large and rapidly growing population that is in need of an alternative. Given the incontrovertible shortage of transplant donors, the prospect of permanent mechanical circulatory assistance or circulatory support as a therapeutic option is compelling.

For widespread use, an LVAD must be easily worn, portable, silent, and not noticeable by the patient. The abilities to alter flow according to demand and to wean slowly before removal are also great advantages. For bridge to myocyte recovery, the device must be mechanically reliable for at least 12 months and be easy to remove. Our elective explants of the Jarvik 2000 Heart proved relatively simple through a limited left thoracotomy without cardiopulmonary bypass; they were followed by rapid recovery of the animals. We found no adverse sequelae from capturing all transmural blood flow with a continuous-flow device. The animals behaved normally, and many recovered uneventfully from a major surgical procedure with predominantly pulseless flow. The effects of a temporary lack of pulsatility in the circulation need to be explored further in humans through neurohormonal studies. Our original intention for long-term circulation need to be explored further in humans through neurohormonal studies. Our original intention for long-term

Evidence to support the “keep your own heart” (myocyte recovery) strategy continues to accumulate, although most reports are anecdotal and without detailed physiological studies. In contrast to the modest pharmacological reductions in ventricular filling pressure and volume, mechanical blood pumps have the capacity to completely offload the left ventricle while the patient remains active. After mechanical bridge to transplantation, the hearts of patients with end-stage idiopathic cardiomyopathy reverted to a normal size and weight. In many patients, indices of left ventricular function approach normal values by the time a donor organ becomes available. Levin and colleagues studied the end-diastolic pressure-volume relationships in excised hearts from transplant recipients with idiopathic dilated cardiomyopathy. They compared cardiac function between those who had received intensive medical management alone versus mechanical circulatory support. Prolonged LVAD use greatly reduced the left ventricular end-diastolic dimensions and pressure-volume relationships. Left ventricular mass was reduced substantially in the LVAD group. The authors concluded that severe left ventricular dilatation in idiopathic cardiomyopathy could be substantially reversed by mechanical unloading.

Frazier and colleagues took tissue samples from the core of the left ventricular apex removed at the time of LVAD implantation and compared them with myocardium from the explanted heart at transplantation. Histological studies showed a marked reduction in the extent of myocytolysis, whereas deranged calcium uptake and binding rates in the sarcoplasmic reticulum were found to have normalized. These features were associated with clinical and radiological improvements together with reduction of plasma norepinephrine levels to near normal. Changes in intracellular calcium concentration have been linked with apoptosis in tumor cells as well as in the heart failure myocyte. Calcium channel blockers have been shown to delay apoptosis; recent studies on the response of myocytes to stress factors suggests an association of apoptosis with the progression of cardiomyopathy. Transient myocardial pressure overload induces the expression of proto-oncogenes, which leads to compensatory hypertrophy of myocytes. It is possible that left ventricular unloading with an LVAD would reverse this process.

Westaby and colleagues performed detailed echocardiographic studies of left ventricular function in patients with end-stage dilated cardiomyopathy not listed for cardiac transplant and treated with a permanent LVAD. With the LVAD briefly switched off, a progressive increase in myocardial contractility was observed, beginning as early as 4 weeks postoperatively.

Müller and colleagues, in Berlin, committed 17 dilated cardiomyopathy patients to the bridge to myocyte recovery strategy using pusher-plate LVADs. Five had significant recovery and were weaned from mechanical support at between 160 and 794 days. Six died during mechanical support, and 4 were received a transplant. Two remained on the device. Disappearance of the autoantibody against the β1-adrenergic receptor was used to time device removal, and left ventricular recovery was sustained. At the same center, 2 infants with acute viral myocarditis and ejection fraction <15% underwent cardiopulmonary resuscitation and then implantation of the extracorporeal “Berlin” left and right ventricular assist devices. They were successfully weaned at 25 and 31 days, with sustained ejection fractions of 55% and 65%, respectively, thus avoiding transplantation. These infants now have normal left ventricular function.

The potential costs for the bridge to myocyte recovery strategy need not be excessive. Gelijns and colleagues, from the Columbia-Presbyterian Hospital, reported similar costs for long-term outpatient treatment with the HeartMate vented electric LVAD as for cardiac transplantation. Ultimately, long-term mechanical cardiac assistance may prove to be less expensive than cardiac transplantation or the intensive medical treatment of patients in NYHA classes III and IV.

A structured clinical program of mechanical bridge to myocyte recovery requires a user-friendly blood pump and pharmacological or genetic strategies to sustain recovery. Some of these prerequisites are now in place. The remainder will emerge with human experience.
Acknowledgments
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References
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