Reliable long-term non-pulsatile circulatory support without anticoagulation

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Abstract

Objective: The Terumo implantable left ventricular assist system (T-ILVAS) consists of a titanium centrifugal pump with a unique magnetically suspended impeller producing continuous (non-pulsatile) flow up to 10 l/min. The interior surface is heparin-coated and there is no purge system. We implanted the device into six sheep to ascertain in-vivo haemodynamic function, mechanical reliability and biocompatibility.

Methods: The T-ILVAS was implanted via left thoracotomy without cardiopulmonary bypass. The inflow cannula was placed in the left ventricular apex and a Dacron outflow graft anastomosed to the descending aorta. All animals recovered well. No anticoagulation (heparin or warfarin) was given after the surgery. Suspension position, motor current, impeller speed and pump flow were continuously monitored and stored by on-line computer. Serial blood samples were collected to determine haematological and biochemical indices of renal function, liver function and haemolysis. All animals were electively euthanized between 3 and 7 months postoperatively. The explanted pumps were examined for mechanical reliability and thrombus formation. Major organs were examined macroscopically and histologically for thromboembolism.

Results: All animals appeared completely normal for up to 210 days. At speeds between 1500 and 2000 rev./min the device pumped up to 8 l/min capturing all mitral flow. There were no major complications (pump failure, thromboembolism, haemorrhage, or driveline infection). Indices of haemolysis, liver and renal function remained within normal limits. All pumps were mechanically sound and free from thrombus. One embolus was found in a sectioned kidney. Conclusion: The T-ILVAS successfully supported the systemic circulation without anticoagulation for up to 210 days. Mechanical reliability and biocompatibility were demonstrated. Organ function remained within normal limits during continuous non-pulsatile flow.

Keywords: Left ventricular assist device; Centrifugal pump; Sheep

1. Introduction

Current centrifugal pumps used for cardiopulmonary bypass, extracorporeal membrane oxygenation and short term circulatory support have a drive shaft and seal subject to blood leakage and thrombus formation [1,2]. These conventional rotary blood pumps have limited durability of the bearings and seal and require continuous heparinization or purge systems. This limits their use for long-term assisted circulation, whilst heat generation at the bearings may denature plasma proteins and predispose to thromboembolism.

Since 1995 the research group of the Terumo Corporation, Japan have sought to overcome the drive shaft and bearing problem by developing a magnetically suspended centrifugal pump (MSCP), the impeller of which is suspended by a magnetic field within the housing [3]. Because the MSCP provides contact free rotation of the impeller without material wear, it is expected to be one of the most durable blood pumps. Early prototypes of MSCP have already operated for more than 2 years in an ex vivo animal model [4,5]. Early experience with intrathoracic implantation of a second generation device (Model 2 MSCP) was terminated because of blood leakage through an intrahousing connector. However, the compact device fitted easily into the thorax of a 45-kg sheep and operated without thrombus formation or thromboembolism. After introduction of a dual connector system and sensorless motor the modified model 2 (Model III) was able to operate in vivo for more than 14 months without any sign of mechanical failure or thromboembolism [4,5]. The MSCP

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now has significant potential for long-term use as an implantable circulatory assist system.

2. Materials and methods

2.1. The Terumo implantable left ventricular assist device (T-ILVAS)

The Terumo implantable left ventricular assist device system (T-ILVAS) is the newest version of the MSCP. The TILVAS is a composed of four parts, the magnetic bearing, an impeller, the housing, and a DC brushless motor (Fig. 1). The impeller rotates through a magnetic coupling between the impeller and the motor and is suspended magnetically by the three electromagnets. The electric current is controlled by the three position sensors to maintain the impeller floating free at the centre of the pump housing. The pump has a displacement volume of 180 ml and weight of 400 g. The blood contacting surface and the inflow and outflow cannulae are modified with a heparin immobilization technique.

2.2. Animal experiments

Between December 1999 and March 2000, six T-ILVAS were implanted into Welsh mule sheep weighing between 70 and 90 kg. All animal data were prospectively entered into a database to record device-related morbidity and mortality, non-device-related morbidity and mortality, pump function (driving speed and energy consumption), and autopsy findings.

Blood samples were collected serially to determine haematological and biochemical indices, prothrombin times, and markers of haemolysis. The surgical procedures and post-operative care were undertaken humanely by licensed personnel in compliance with United Kingdom Home Office guidelines.

2.3. Operation

The sheep were anaesthetized with thiopentone then intubated and ventilated with halothane in oxygen. A thermo-
dilution pulmonary arterial catheter and arterial cannula were introduced into the left internal jugular vein and the left common carotid artery, respectively.

The animals were positioned for left thoracotomy. The sixth intercostal space was entered to provide access to both the apex of the left ventricle and the descending thoracic aorta.

The Dacron velour-covered power cable was first tunnelled under the scapula towards the midline to exit the skin of the left flank. The power line was then connected externally to the control system and power supply. Attention was then turned to the descending thoracic aorta which was partially mobilized for the outflow graft anastomosis. An aortic side clamp was applied and a 1.5-cm linear incision made in the vessel wall. To this the pre-clotted Dacron outflow graft of the device was anastomosed with 3-0 polypropylene.

The pericardium was then opened to gain access to the apex of the left ventricle. The apex was elevated and circumscribed with interrupted Teflon-pledgetted mattress sutures of 2-0 Tycron. These were used to secure the inflow cuff of the device. A cruciate incision was made into the apical muscle and the inflow cannula of the TILVAS (Fig. 2) easily inserted without blood loss. This was secured with a tape around the apical cuff to align the inflow cannula axially within the left ventricular cavity. The system was carefully de-aired before releasing the clamp on the outflow graft and switching the device on at a speed between 1000 and 2500 rev./min. With the pump in situ we implanted an ultrasonic flow probe around the outflow graft to determine pump flow at different rotational speeds. With normalized circulating blood volume and central venous pressure we determined the pump speed (1800–1900 rev./min) at which the aortic valve remained closed through capture of all transmitral flow. At greater speeds pulse pressure disappeared from the systemic circulation. An intercostal drain was inserted and the wound then closed in layers. Anaesthesia was discontinued and the sheep transferred from the operating room to the pen.

2.4. Recovery

The sheep were extubated after 30–60 min of spontaneous respiration after documentation of satisfactory blood gases and acid–base balance. A vest was placed around the thorax to carry the controller and connect with the electrical power line. The animals were then allowed to mobilize, drink, feed, and roam around the sheep pen. Indwelling carotid arterial and jugular venous lines were left in situ in all animals for 48 h. These were used to continuously monitor arterial and venous pressure and to ensure that pump flow abolished left ventricular ejection through the aortic valve. Under these conditions blood flow was through the pump and entirely non-pulsatile. This flow rate was maintained and the animals observed for adverse neurological or renal effects of non-pulsatile flow. Prior to sacrifice the non-pulsatile status was again confirmed by invasive monitoring.

Neurological status was determined after recovery from anaesthetic by observing behaviour, mobility and balance. Renal and hepatic function were assessed serially by measurement of blood urea, creatinine, bilirubin and liver enzymes. After removal of the indwelling lines, blood samples were obtained by direct puncture of the internal jugular vein. Pump speed and power requirements were recorded twice daily. Auscultation was used to check the tone of the device. Neither heparin nor warfarin were used for anticoagulation after the surgical procedure.

2.5. Studies of safety, efficacy and long-term reliability

Data from device including motor suspension current, energy requirement and calculated pump flow were monitored constantly by on-line computer. Mechanical reliability was determined by recording parameters of pump function, by auscultation of the chest, and by inspection of power lines and driveline exit site. The sheep were examined for signs of heart failure, thromboembolism or abnormal behavior.

2.6. Device retrieval and autopsy studies

Four sheep were electively euthanized at 90 days after implantation. One was electively euthanized at day 210 and another at 360 days.

Prior to sacrifice at 3 months the sheep were given heparin (5000 IU/kg) intravenously to avoid clot formation on the blood-contacting surfaces of the pump and cannulae. After elective sacrifice the pump and vascular graft were removed by careful dissection. The interior of the native heart, vascular graft and aortic anastomosis were examined for thrombus formation. The pump was then perfusion-washed with saline by pumping at 2000 rev./min followed by fixation with 2% glutaraldehyde solution. The pump and computer were then returned to the Terumo Corporation for disassembly and inspection for mechanical wear, thrombus formation and component reliability.

Detailed post mortem examination was performed with macroscopic and histologic examination of the sheep aorta, carotid and renal arteries, together with kidney, liver, lungs and brain.

2.7. Statistical analysis

All results for continuous variables are expressed as mean ± standard deviation. The Student’s paired or unpaired t-test, or Mann–Whitney test if appropriate, were used to compare continuous variables between two subgroups. P-values of less than 0.05 were considered to indicate statistical significance.
3. Results

3.1. Mortality and morbidity

All six animals recovered rapidly after TILVAS implantation. Two sheep suffered ventricular fibrillation during surgery but were successfully defibrillated and recovered well. All wounds healed without complications and there were no driveline infections. All animals survived in excellent condition prior to elective termination. During this time all systemic blood flow was provided by the TILVAS without anticoagulation.

3.2. Hemodynamic studies

Hemodynamic studies before chest closure showed the relationship between pump speed (rev./min) and cardiac output. Systemic blood flow was observed to be non-pulsatile at pump rates exceeding 1500 rev./min (Fig. 3).

3.3. Device reliability

Power consumption for both magnetic suspension and impeller rotation was 8–10 W. All but one device performed continuously and consistently as determined by auscultation of the chest and analysis of the computer recordings. Except for this one case, the impeller position measured by the three sensor output remained at the centre of the housing with an axial excursion of less than 0.25 mm despite vigorous movements of the sheep around the pen. The surface temperature of the motor and the electromagnets remained at 38–42°C throughout the duration of all experiments. No thrombus formation was found in the TILVAS or vascular graft despite the fact that the sheep did not receive any anticoagulation (Fig. 4). None of the sheep suffered bloodborne infection or device endocarditis.

One device performed erratically for 18 h (3 weeks after implantation), then spontaneously reverted to normal function. During this period the impeller lost its central position, stopped temporarily then restarted, initially with contact of the impeller against the housing. This could be heard with the stethoscope. Autopsy on this animal 10 weeks later subsequently showed that the rigid inflow cannula had abutted onto the interventricular septum, probably resulting in thrombus formation at this site. We speculate that thrombus had been sucked into the pump causing temporary dysfunction. This hypothesis was reinforced by the autopsy finding that the upper pole of one kidney had suffered infarction.
3.4. Indices of haemolysis

Daily observation showed the urine to be clear. Intermittent random testing showed no haemoglobinaemia. Weekly blood tests showed the haemoglobin level to remain constant with no significant rise in lactate dehydrogenase after the peri-operative period. Plasma free haemoglobin levels are shown in Table 1. These remained < 5 mg/dl apart from the early postoperative period when factors such as non-cross-matched blood transfusion caused some haemolysis.

3.5. Renal and hepatic function

Weekly blood tests showed the blood urea and creatinine levels to remain stable and within the normal limits (Table 2). Indices of hepatic function are shown in Table 3. After modest early post-operative changes hepatic function remained normal for the duration of the study.

4. Discussion

Whilst a complex device in bio-engineering terms, the magnetically suspended impeller is one of the most promising approaches towards mechanical reliability and non-thrombogenicity in a centrifugal blood pump. The contact-free impeller overcomes potential problems of bearing wear and heat generation and does not require purge fluid. Our time-limited investigations and Terumo’s own trial out to 864 days show excellent blood compatibility without haemolysis [4]. Intracardiac thrombus probably occurred in one of our sheep through an adverse position of the rigid inflow cannula. There was no thrombus within the pump itself and there has been no thrombus formation or thromboembolism in other sheep. Whilst prototype models suffered mechanical problems, the current device is reliable [5]. As a result of our experiments we have suggested a different inflow cannula design for the human model.

Until recently it was inconceivable that a rotary blood pump could function for years in the circulation without anticoagulation, thrombus formation or thromboembolism. The new blood pumps (Jarvik 2000 and TILVAS) are extremely promising in this respect, and we expect them to become the first realistic devices for permanent mechanical circulatory support [6]. Currently we suggest that these left ventricular assist devices are positioned in the left pleural cavity bridging between the apex of the dilated left ventricle and the descending thoracic aorta.

This position allows for short vascular outflow graft, and leaves the mediastinum clear in the event of subsequent cardiac transplantation. It also avoids a potentially thrombogenic cul-de-sac in the aortic root as may occur when an outflow graft is joined to the ascending aorta when the valve remains permanently closed. Similarly, intrapleural placement on the diaphragm avoids the need to open the abdominal cavity either during implantation or device removal. This reduces the amount of surgical trauma and expedites recovery by avoiding gastrointestinal ileus and delayed feeding.

In practice it is now evident that the patient with a non-pulsatile pump can develop pulsatility in the systemic circulation within hours or days of left ventricular unloading. Our experience with our first two Jarvik 2000 heart patients has confirmed an early return to pulsatility even in absolute end-stage dilated cardiomyopathy [7]. This, together with positive outcomes after prolonged non-pulsatile flow in the sheep model, gives us confidence that both axial flow and centrifugal blood pumps will provide safe and effective long-term circulatory support in the patient with heart failure.

In conclusion, The TILVAS is a novel and effective non-pulsatile blood pump which performs reliably without anticoagulation in the sheep model.

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Table 1
Indices of haemolysis in six sheep with the Terumo implantable left ventricular assist system (T-ILVAS)$^a$

<table>
<thead>
<tr>
<th></th>
<th>Pre-op.</th>
<th>7 days</th>
<th>30 days</th>
<th>60 days</th>
<th>90 days</th>
<th>180 days</th>
</tr>
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<tbody>
<tr>
<td>n</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>Hb (g/dl)</td>
<td>12.6 (0.3)</td>
<td>10.8 (1.4)</td>
<td>9.9 (1.0)</td>
<td>11.1 (1.2)</td>
<td>11.6 (1.1)</td>
<td>11.6 (1.1)</td>
</tr>
<tr>
<td>Pl-Hb (mg/dl)</td>
<td>4.9 (2.5)</td>
<td>8.7 (4.0)</td>
<td>3.3 (2.6)</td>
<td>6.1 (4.7)</td>
<td>5.0 (3.2)</td>
<td>4.8 (2.6)</td>
</tr>
<tr>
<td>LDH (U/l)</td>
<td>471 (76)</td>
<td>912 (266)</td>
<td>738 (100)</td>
<td>500 (70)</td>
<td>500 (65)</td>
<td>491 (94)</td>
</tr>
</tbody>
</table>

$^a$ Values are mean (SD). Hb, haemoglobin; Pl-Hb, plasma haemoglobin; LDH, lactate dehydrogenase.

Table 2
Indices of renal function in the T-ILVAS sheep$^a$

<table>
<thead>
<tr>
<th></th>
<th>Pre-op.</th>
<th>7 days</th>
<th>30 days</th>
<th>60 days</th>
<th>90 days</th>
<th>180 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urea (U/l)</td>
<td>3.3 (0.5)</td>
<td>3.8 (0.7)</td>
<td>3.0 (2.2)</td>
<td>4.5 (65)</td>
<td>11.6 (1.1)</td>
<td>3.9 (9.2)</td>
</tr>
<tr>
<td>Cr (μmol/l)</td>
<td>76 (21)</td>
<td>86 (10)</td>
<td>92 (16)</td>
<td>71 (29)</td>
<td>85 (7.2)</td>
<td>75 (26)</td>
</tr>
</tbody>
</table>

$^a$ Values are mean (SD). Cr, creatinine.
References


Appendix A. Conference discussion

Dr C. Baufreton (Angers, France): Could you tell me what kind of heparin coating was used in this device? And a second question, did you assess whether this type of heparin coating remained stable over the time during this implantation? Did you realize specific analysis to assess that stabilization of the heparin coating?

Dr Saito: For the first question, the only heparin we gave in these animal studies was 3000 units during surgery. That is all. And so far as our examination of the inside the device is concerned, the heparin-coating system was stabilized. This is not a large number, but as far as we can tell, the detailed study of the surface of the device using the electron microscope showed the stability of the heparin-coated system.

Dr O. Frazier (Houston, TX, USA): What was the appearance of the aortic valve and the myocytes at the time of sacrifice?

Dr Saito: Well, as you know, the sheep left ventricle is quite small, but this device is so powerful, it sucked all the blood into this device. The aortic valve always remained closed.

Dr Frazier: What did it look like at sacrifice?

Dr Saito: At sacrifice, grossly there was no fusion of the aortic valve leaflets but microscopically the aortic wall was thinner than normal.

Table 3
Indices of hepatic function in the T-ILVAS sheep

<table>
<thead>
<tr>
<th></th>
<th>Pre-op.</th>
<th>7 days</th>
<th>30 days</th>
<th>60 days</th>
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<td>6</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>T-Bil (Umol/l)</td>
<td>2.0 (0.8)</td>
<td>5.5 (2.9)</td>
<td>3.3 (1.7)</td>
<td>1.6 (0.6)</td>
<td>2.0 (0.2)</td>
<td>1.8 (0.4)</td>
</tr>
<tr>
<td>GPT (IU/l)</td>
<td>49 (35)</td>
<td>29 (8.7)</td>
<td>16 (8.1)</td>
<td>15 (2.4)</td>
<td>14 (2.4)</td>
<td>14 (1.7)</td>
</tr>
<tr>
<td>GOT (IU/l)</td>
<td>84 (24)</td>
<td>255 (49)</td>
<td>60 (4.9)</td>
<td>69 (9.7)</td>
<td>74 (12)</td>
<td>68 (12)</td>
</tr>
<tr>
<td>γ-GTP (IU/l)</td>
<td>47 (6)</td>
<td>51 (12)</td>
<td>58 (5.6)</td>
<td>46 (13)</td>
<td>49 (15)</td>
<td>50 (16)</td>
</tr>
</tbody>
</table>

Values are mean (SD). T-Bil, total bilirubin; GPT, serum glutamate pyruvate transaminase; GOT, serum glutamate oxalate transaminase; γ-GTP, gamma-guanosine triphosphate.